Department of Health Protection
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and

Department of Public Health
University of Helsinki

Economic evaluations in adopting new vaccines in the Finnish national vaccination programme

Heini Salo

ACADEMIC DISSERTATION

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Supervisors
Professor Terhi Kilpi
Department of Health Protection
National Institute for Health and Welfare

Professor Emeritus Harri Sintonen, PhD
Department of Public Health
University of Helsinki

Reviewers
Professor Harri Saxén
Children's Hospital
Helsinki University Hospital

Associate Professor Anthony Newall
School of Public Health and Community Medicine
University of New South Wales Australia

Opponent
Assistant Professor Alessia Melegaro
Department of Policy Analysis and Public Management
Università Bocconi

Custos
Professor Juha Pekkanen
Department of Public Health
University of Helsinki

Cover graphic: Jari Salmela

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Contents

Abstract

In Finland the economic evaluation of the vaccination programme has been part of the decision-making process since 2001. After 2003, five vaccinations have been considered for the Finnish national immunisation programme (NVP) and for which an economic evaluation has been conducted. This study presents the materials, methods, and results of the economic evaluations of 7-valent pneumococcal conjugate vaccination (PCV7) and influenza vaccination programmes and human papillomavirus (HPV)-associated cost of illness study, all of which were used in the vaccine adoption decision-making process in Finland in 2001–2011.

When a new vaccine is considered for inclusion into the NVP in Finland the expected public health benefit, the safety of the vaccine for an individual, the safety of the vaccination programme at the population level, and the cost-effectiveness of the vaccination programme are evaluated. An economic evaluation is needed to support the decision-making process. The decision-makers have not specified an explicit range of cost-effectiveness threshold values below which an intervention would automatically be accepted and lead to funding.

In the first economic evaluation of the infant PCV7 vaccination programme (excluding indirect herd effects) the cost per QALY gained was EUR 54 600. The decision-makers concluded that the programme was not cost-effective. In the economic re-evaluation, including the indirect herd effects of the vaccination programme in older age groups reduced the cost per QALY gained to EUR 20 600. Thus, infant pneumococcal vaccinations were accepted into NVP in 2010.

The influenza vaccination programme of healthy children was found to yield cost savings from the health care provider perspective even though the indirect herd effects and influenza-associated deaths were excluded. The vaccination programme was estimated to save annually EUR 7.6 per vaccinated child aged 0.5–4 years when the assumed vaccine efficacy was 60%. Thus vaccinations of all children aged 6–36 months with influenza vaccine were accepted into the NVP in 2007.

In Finland, there is a considerable annual disease burden of HPV-related genital disease in the female population. Most of it is detected by the 446 000 annual screening tests, 55% of which are carried out as opportunistic tests. It is noteworthy that the opportunistic tests account for 71% of the total of EUR 22.4 million screening costs. Considering all tests taken both within and outside the organised programme, the 5-year coverage of Pap testing in Finland was 87% among women aged 25–69 years. Further diagnostics, management and treatment of HPV-related genital disease resulted in an additional cost of EUR 22.3 million, of which the costs of less severe HPV-related disease manifestations were EUR 15.5 million.

At present, 60% of Pap tests detecting most of the cervical cancer and intraepithelial neoplasia cases in Finland are carried out outside the organised programme. Thus, the successful reduction in the cervical cancer incidence and mortality is due to tests taken both

within and outside organised screening. Opportunistic Pap testing both substitutes and overlaps with the tests taken within the organised programme. Overlapping tests stem from the lack of coordination between organised and opportunistic Pap testing and result in overmanagement of reversible lesions. In order to be able to coordinate organised and opportunistic Pap testing, it is essential to establish a nationwide Pap test register. Likewise, it is important not to lose the high coverage when trying to achieve reductions in overlapping Pap testing. Furthermore, such a register is necessary for the effective and cost-effective secondary prevention of cervical cancer, which will be needed in both unvaccinated and vaccinated populations.

The estimates produced in the disease burden and costs of HPV-related genital disease in women and the overall coverage, frequency and costs of Pap testing were further used as data in the HPV transmission and progression model and in the economic evaluations of the HPV vaccination programme and screening of cervical cancer. Vaccinations of all girls aged 11–13 years with HPV vaccine was estimated to yield cost-savings and was accepted into the NVP in 2013.

List of original publications

This thesis is based on the following articles, which are referred to in the text by the numerals I, II, III and IV. Unpublished data are also presented.

I. Salo H, Sintonen H, Nuorti JP, Linna M, Nohynek H, Verho J, Kilpi T. Economic evaluation of pneumococcal conjugate vaccination in Finland. Scand J Infect Dis. 2005;37(11-12):821-32.

II. Salo H, Kilpi T, Sintonen H, Linna M, Peltola V, Heikkinen T. Cost-effectiveness of influenza vaccination of healthy children. Vaccine. 2006 Jun 5;24(23):4934-41.

III. Salo H, Leino T, Kilpi T, Auranen K, Tiihonen P, Lehtinen M, Vänskä S, Linna M, Nieminen P. The burden and costs of prevention and management of genital disease caused by HPV in women: a population-based registry study in Finland. Int J Cancer. 2013 Sep 15;133(6):1459-69.

IV. Salo H, Nieminen P, Kilpi T, Auranen K, Leino T, Vänskä S, Tiihonen P, Lehtinen M, Anttila A. Divergent coverage, frequency and costs of organised and opportunistic Pap testing in Finland. Int J Cancer. 2014 Jul 1;135(1):204-13.

Abbreviations

AIS	adenocarcinoma in situ
AOM	acute otitis media
CAP	community-acquired pneumonia
CBA	cost-benefit analysis
CEA	cost-effectiveness analysis
CIN	cervical intraepithelial neoplasia
CUA	cost-utility analysis
FinOM	Finnish otitis media
HPV	human papillomavirus
ICD-10	International Classification of Diseases 10th revision
ICER	incremental cost-effectiveness ratio
IPD	invasive pneumococcal disease
KRAR	National Advisory Committee on Vaccinations
LAIV	live attenuated influenza vaccines
LYG	life-years gained
MSAH	Ministry of Social Affairs and Health
NCKP	Northern California Kaiser Permanente
NVP	National Vaccination Programme
NITAG	National Immunisation Technical Advisory Group
NVT	non-vaccine serotype
OSF	official statistics of Finland
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PPV	pneumococcal polysaccharide vaccine
QALY	quality-adjusted life-year
SII	Social Insurance Institution
THL	National Institute for Health and Welfare
TIV	trivalent inactivated influenza vaccine
VaIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia
VT	vaccine serotype

1 Introduction

1.1 National vaccination programme in Finland

The aim of the national vaccination programme (NVP) is to provide the best possible protection for the Finnish population against vaccine-preventable diseases. The NVP started to take shape in the late 1950s when well-baby clinics covered almost the whole country. In Finland, all childhood vaccinations are provided in well-baby clinics or school health care clinics, both of which are part of public primary health care. Vaccinations are free-of-charge and voluntary.

In 2006 all children were offered protection against eight diseases: diphtheria, tetanus, pertussis, polio, severe infections caused by *Haemophilus influenzae* type b, measles, mumps, and rubella (1). In addition, vaccination against tuberculosis, hepatitis A and B, seasonal influenza and tick-borne encephalitis were offered to special risk groups. After 2006, three new vaccines were introduced into the NVP. Vaccinations against infections caused by rotavirus and pneumococcus were introduced in 2009 and 2010, respectively. Vaccination against infections caused by human papillomavirus has been provided for all girls since 2013. In addition, eligibility criteria for seasonal influenza vaccine were extended in 2007 to include all children aged 6–36 months.

1.2 Decision-making

The Ministry of Social Affairs and Health (MSAH) is authorised by law to make decisions concerning the NVP after consultation with the National Institute for Health and Welfare (THL). THL is the expert institution on vaccinations in Finland, which guides, develops and supports the NVP. THL 1) supports decision-making concerning the NVP, 2) co-ordinates the work done at the THL-appointed vaccine-specific working group and at the National Advisory Committee on Vaccinations (KRAR), 3) studies and evaluates the vaccine-preventable burden of disease, 4) monitors and assesses the population-level effects of vaccinations (burden of disease, immunology, safety, cost-effectiveness) by means of the national vaccination register and other health care registers, 5) produces and disseminates information on vaccinations, and collaborates with the public health centres responsible for carrying out vaccinations, and 6) procures and distributes the vaccines included in the national vaccination programme.

THL appoints the National Advisory Committee on Vaccinations (KRAR) that oversees the international development of vaccines and vaccination programmes, supports THL and MSAH in the development of NVP and the preparation of decisions, and gives THL general guidance and recommendations on vaccinations both within and outside the NVP.

MSAH is the decision-making authority on the NVP in Finland and is responsible for combating communicable diseases and widespread diseases in the Finnish population. MSAH appoints an Advisory Board on Communicable Diseases that is the national expert body for combating communicable diseases, thus 1) monitoring the general development of communicable diseases, 2) supporting the preventive health services and 3) making statements on the NVP.

Figure 1 illustrates the current decision-making process for adopting a new vaccine into the NVP. When the need for an evaluation is acknowledged, for example, because a new vaccine is coming into the market or there is a potential change in the benefit-risk ratio of the vaccination programme (e.g. change in disease incidence, vaccine effectiveness or safety), a vaccine-specific working group is established by THL. The working group is composed of national experts on vaccines and vaccinations, infectious diseases, epidemiology and health economics. It may also consult individual experts or pharmaceutical companies if needed. The working group carefully evaluates the potential vaccination programme according to four criteria given by KRAR: 1) expected public health benefit, 2) safety of vaccine for an individual, 3) safety of the vaccination programme at the population level, 4) cost-effectiveness.

To be able to determine the expected public health benefit, the working group needs data on the burden of disease in Finland, the efficacy of the vaccine in the target group and the effect of vaccinations on the whole population. The incidence of the infectious disease, mortality, life years lost and the use of health care services are estimated from health care registers. Also, health-related quality-of-life losses due to the disease are estimated. To evaluate the direct and indirect effect of vaccinations on the population, a dynamic transmission model of the disease is required (2). The effectiveness among the vaccinated and unvaccinated (potential indirect effects) population is evaluated separately (3). In some cases, the expected public health benefit can be considerable only in a sub-population with a higher risk of disease than the general population. For example, individuals with certain medical conditions have a higher risk of complications associated with influenza and people living in some geographical areas are more likely to contract tick-borne encephalitis than the population in general.

The safety of the vaccine for an individual and the safety of the vaccination programme at the population level are evaluated. The population-level safety of a vaccination programme may be jeopardized through indirect effects of vaccinations (e.g. shift of disease to older age groups or replacement of the eliminated microbe by another capable of causing disease)(4-8). These potential indirect effects in the population can be investigated using dynamic transmission models (3, 9).

For a new vaccine to be accepted into the NVP it must have been assessed to be cost-effective. Yet, the decision-makers have not specified an explicit range of threshold values in Finland for a cost per QALY gained what should be considered cost-effective. This may jeopardize the transparency of decision-making. The cost-effectiveness analyses are done in

the Department of Health Protection at THL. In order to maintain the independence of the analyses, they have been financed by the State Budget. The cost-effectiveness analyses can be done from the health care provider perspective and from the societal perspective, if deemed helpful to the decision-making. The effectiveness of the vaccination programme is measured both in life years gained (LYGs) and quality-adjusted life years (QALYs) gained.

A Working Group recommendation is presented to the National Advisory Committee on Vaccination (KRAR) summing up the expert opinion. THL gives its recommendation to MSAH after hearing the expert opinion of the Working Group and KRAR. The decision on the introduction of a new vaccine into the NVP is finally made by MSAH when it has received the THL recommendation and consulted its Advisory Board on Communicable Diseases. The decision on funding is made by the Finnish Parliament. After the decision-making process has been completed, it is the responsibility of THL to implement any changes.

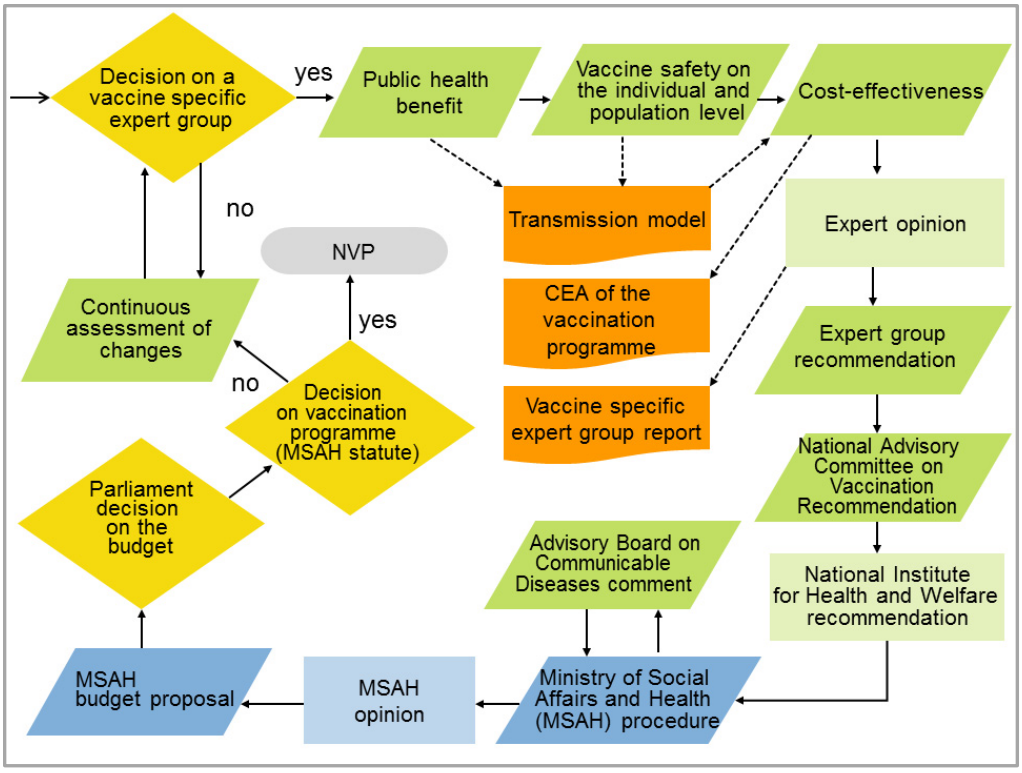

Figure 1. Decision-making process for adopting a new vaccine into the national vaccination programme (adapted from (10)).

1.3 Resources, costs, and funding of the national vaccination programme

The vaccines of the NVP are purchased centrally and funded by the government budget. Due to the introduction of new vaccines, government budget appropriations for vaccine purchases have increased from EUR 5.3 million in 2001 to EUR 10.6 million in 2007 and further to EUR 22.9 million in 2014. These figures do not include supplemental funds for pandemic flu vaccines.

The budget appropriation is used for the 1) purchase, storage and distribution of vaccines, 2) guidance on vaccine usage, 3) investigation of the epidemiological and immunological impact, coverage and safety of vaccinations as well as the development of their surveillance systems, 4) management of obligatory storing system, 4) the payment of the Finnish Co-operative for Pharmaceutical Injury Indemnities, and 5) procurement costs.

All vaccines for the NVP are purchased according to an open EU-tender procedure. The storage and distribution of vaccines is outsourced to a wholesale distributor of pharmaceutical products. Vaccines are distributed to hospital pharmacies and pharmaceutical centres, which reallocate the vaccines to the municipal health care centres where the vaccinations are carried out.

When the introduction of a new vaccine into the NVP is considered, THL researchers and experts compile the data that the vaccine-specific working group needs to be able to form the required expert opinion. Approximately 4 full-time equivalent employees (equivalent to EUR 240 000) are allocated annually to the evaluation of vaccination programmes at THL. The work of the members of vaccine-specific working groups that are not THL employees is not included in this figure. Each member is compensated for a meeting by a nominal fee totalling from EUR 1200 to EUR 26 000 per working group.

In addition to the cost of vaccines there are also other costs related to the introduction of a new vaccine. These costs include the administrative costs of vaccinating, e.g. supplies and time nurses spend on the routine activities of vaccinating, as well as on information dissemination. THL provides information on the new vaccine programme to health care workers and to target groups. It is essential to assess the feasibility and acceptability among health care workers and those to be vaccinated to achieve a good vaccination coverage.

Approximately 4 full-time equivalent employees (equivalent to EUR 240 000) are allocated annually to the implementation of vaccination programmes at THL. In addition, wider media campaigns have been launched for seasonal influenza and HPV vaccination programmes. The annual costs of the materials (e. g. posters, handouts, and brochures) for the seasonal influenza vaccination campaign have been on average EUR 27 000. In 2015–2016 the costs of materials were considerably higher (EUR 60 000) after the live attenuated influenza vaccine (LAIV) was implemented for two-year-olds for the first time. Half of the costs were accounted for by a survey of public health nurses and parental knowledge and attitudes towards intranasal LAIV. In addition to these marginal costs, there are fixed costs that are

covered by the already existing public health care system (well-baby clinics and school health care clinics provided by local municipalities) that carries out all vaccinations in the NVP in Finland.

According to the Communicable Diseases Act (1986/583, revision 2010/1244), THL shall monitor the efficiency and effects of the vaccines used for the prevention of communicable diseases. The surveillance of infectious diseases is conducted through health care registers held by THL. The National Infectious Diseases Register is based on the notifications of cases of generally hazardous or notifiable communicable diseases. In 2016 eight full-time equivalent employees (equivalent to EUR 480 000) are allocated annually to maintain the National Infectious Diseases Register at THL. The Care Register for Health Care (former Hospital Discharge Register) contains data on inpatient care and secondary outpatient care. The National Vaccination Register is used in the follow-up of vaccination coverage, safety, and effectiveness. The Vaccine Adverse Effects Register is a spontaneous vaccine safety surveillance system relying on passive reporting of events suspected by reporters to be vaccine related. THL keeps all the before-mentioned registers. The Vaccine Adverse Effects Register is going to be transferred to the care of the Finnish Medicines Agency when the new Communicable Diseases Act enters into force in March 2017. The epidemiological surveillance of adverse effects will remain at THL.

This thesis describes the disease burden and cost-effectiveness studies related to three vaccines, the introduction of which was considered in Finland during the period 2001–2011. These studies were carried out specifically to provide data to inform decision-making following the process described above. The thesis also shows how the utilization of Finnish registers in estimating the disease burden has improved during the 10-year period in which this study was undertaken.

2 Aims of the study

The purpose of the study was to estimate the burden and costs of three potentially vaccine-preventable diseases and conduct an economic evaluation of two vaccination programmes in Finland. The detailed objectives were:

1) to estimate the burden and costs of potentially vaccine-preventable diseases (pneumococcal diseases, influenza related diseases in children, human papillomavirus related genital diseases in women),

2) to assess the cost-effectiveness of pneumococcal conjugate vaccination programme for infants,

3) to assess the cost-effectiveness of influenza vaccination programme of healthy children.

3 Review of the literature

3.1 Economic evaluation in health care

Decision-makers make choices and decisions on how to allocate scarce resources in health care. Economic evaluations are used as a tool and aid for decision-making in allocating the economic resources as optimally as possible. Information is needed on efficiency, distributional changes, and the fairness of the potential re-allocations following the decisions (11). In the economic evaluation, alternative interventions are systematically compared in regard to both their costs and consequences.

In economic evaluations, both the inputs (costs) and outputs (consequences) of the relevant alternative interventions are evaluated. Different types of economic evaluation measure costs in a monetary value but vary in how the consequences (health effects) of an intervention are evaluated (11). In the cost-benefit analysis (CBA), the health effects are translated into monetary units. In the cost-effectiveness analysis (CEA), the health effects are measured in terms of natural units related to the intervention (e. g. deaths averted, life-years gained). In the cost-utility analysis (CUA) the health effects are measured in terms of combined changes in the quality and quantity of life (mortality), typically expressed in Quality-Adjusted Life-Years (QALYs) gained.

The number of QALYs gained is a widely used effectiveness measure in evaluating health care interventions (11). It is a composite measure that combines both the impact of an intervention on life expectancy (mortality) and health-related quality of life (morbidity). In the QALY framework each period of time in a given state may be assigned a utility value. A scale from zero (representing death) to one (representing full health) has become the conventional scale for QALY weights. The utility value corresponds to health-related quality of life during that period.

In the context of welfare economics, individuals are assumed to be the best experts in judging their own welfare, which is expressed in terms of individual utility (12). Social welfare is the sum of these individual utilities. According to the Pareto principle an improvement in social welfare occurs if an intervention increases the utility of at least one individual without making anyone else worse off. Pareto-efficiency is an allocation of resources to which no reallocation can be made without reducing at least one individual's utility.

In reality there are few situations where an intervention could be judged by the Pareto principle. The acknowledged problem of the Pareto principle is that usually public programmes favour some individuals (gainers) and disfavours others (losers) (12, 13). A less restrictive Kaldor-Hicks criterion has been developed to solve the problem of losers. If after an intervention those who benefit could hypothetically compensate those who lose and still be left better off, the situation would constitute a Kaldor–Hicks improvement or potential Pareto improvement. The compensation does not actually have to take place and the fairness or distribution of utility in society is not taken into account. This constitutes the welfare economic foundation of CBA.

In the welfarist approach, the aim is to maximise overall welfare. Welfarism has been argued as being too narrow an approach, since it is judging social welfare simply in terms of individual preferences (11). Furthermore, there are other things that cannot be ignored in making social choices. There are goods and services that have been considered as so important, even meritorious, to society that it is reasonable to argue that they should be provided or subsidised in a society and special attention should be paid to the equity and equality in their distribution. In practice, concerns about the use of CBA in decision-making regarding publicly funded health care interventions have related to the unwillingness to value the length and quality of life in terms of money and the distributional inequity following from the admitted fact that the willingness-to-pay of welfare is also affected by ability to pay (13, 14).

In the extra-welfarist approach, the aim is usually to maximise just health itself. The extra-welfarist approach also uses other outcomes than utility and other sources of valuation than the affected individuals (15). Furthermore, it weights the outcomes with other than preference-based principles and makes interpersonal comparisons of well-being in a variety of dimensions. In the extra-welfarist approach, the health effects are usually measured as QALYs gained. In a CEA carried out with QALYs from an extra-welfarist perspective, the assessment of social welfare is based on an external evaluation of individuals targeted in the intervention (13).

There are also concerns in the use of CEA with QALYs in evaluating publicly funded health care interventions. The approach has been criticised for ignoring or at least underestimating the non-health benefits of the intervention and for setting maximization of health as the only goal of societal decision-making (13). In addition, CEAs cannot be directly used in decision-making since judging the intervention using the CEA requires a given threshold for the cost per QALY gained when the alternative is more expensive and more effective. Thus, a decision-maker has to specify a threshold value for the incremental cost-effectiveness ratio (ICER) below which the intervention becomes acceptable.

A comparison of interventions has to be made at a single point in time. The future costs and benefits are adjusted for differential timing by discounting, in which case costs and benefits are reduced to the same point of time. Curative and preventive interventions differ in timing. When the costs and benefits of curative interventions occur usually at the same time in

preventive interventions, such as in vaccination programmes, there are usually different time profiles for costs that occur now and benefits that occur in the future (11). Thus, the longer the delay in benefits obtained from the vaccination, the greater is the influence of discounting. In evaluating health interventions, the used discount rate usually rests on the social rate of time preference, which is the rate that reveals society's preferences for consumption in one time period compared with another (16). In addition, there has been much debate on whether both costs and health effects should be discounted at an equal or differential rate. In most countries, the national guidelines recommend equal discounting. However, equal discounting has been criticised as favouring curative interventions over preventive ones. Differential discounting is used at least in Belgium, the Netherlands and Poland (17). Jit and Mibei (18) conclude that compared to equal discounting, differential discounting appears to be fairer from an inter-generational perspective, since discounting will reduce the value of future health and the consumption gains of the current and future generation.

3.2 Direct and indirect effects of vaccination

Prophylactic vaccines are given to non-infected individuals in order to prevent infections. The direct effects of vaccination reduce the susceptibility of a vaccinated individual to contract the infection or disease, or reduce the infectiousness of a vaccinated individual (3, 4). The indirect effects in an individual result from changes in exposure to infection due to the direct effects on the other, vaccinated individuals in the population. The indirect effects affect both vaccinated and unvaccinated individuals.

The direct effect of vaccination is defined as the reduction in the risk of infection in a single vaccinated individual when everyone else remains unvaccinated. The direct effect of vaccination (vaccine efficacy) is typically studied in an individually randomised controlled trial under ideal conditions, where an equality of exposure to infection and a baseline equality between the vaccinated and unvaccinated groups with respect to relevant risk factors can be assumed through randomisation (3).

In practice, many of the effects of vaccination are effects of the vaccination programme. Effects can also be classified according to whether they affect vaccinated or unvaccinated individuals. Figure 2 presents how these effects in vaccinated, unvaccinated, or the whole population are defined, and they can be estimated, at least ideally, by comparing appropriate subgroups (3, 4, 9). The indirect effect on a vaccinated individual is the reduction in the risk of his or her infection due to other individuals being vaccinated in the population. Theoretically it could be estimated by comparing a vaccinated individual in a partially (or even wholly) vaccinated *population A* with a vaccinated individual in *population C*, in which everyone else is unvaccinated. In practice, it may be impossible to distinguish the direct and indirect effects on the vaccinated individual. The total effect of the vaccination on a vaccinated individual is the reduction in the risk of infection due to the direct and indirect effects of the vaccination. It can be estimated by comparing vaccinated individuals in a partially vaccinated *population A* with unvaccinated individuals in an unvaccinated *population B*.

The indirect effect on an unvaccinated individual is the reduction in his or her risk of infection due to vaccinating other individuals in the population. It can be estimated by comparing unvaccinated individuals in a partially vaccinated *population A* with unvaccinated individuals in an unvaccinated *population B*. The total and indirect effects of vaccination on an unvaccinated individual are the same, since an unvaccinated individual does not gain direct protection by the vaccination. Finally, the overall public health effect of the vaccination (effectiveness of vaccination programme) is defined as the weighted average of the corresponding risk reductions due to indirect effects on the unvaccinated individuals and the total effects on the vaccinated individuals.

The protective effect of a vaccination can be measured by the reduction in either acquiring the infection or contracting the symptomatic disease. As an example, the pneumococcal conjugate vaccine (PCV) has been shown to reduce both the nasopharyngeal carriage (19) and invasive disease (20) due to vaccine-type pneumococci. When the indirect effect of vaccination reduces the risk of infection or disease it is called the herd effect. For example, it depends on the direct efficacy, the vaccination coverage, and on how the unvaccinated and vaccinated groups mix in the community. Indirect effects are not always favourable. For example, a shift in the age distribution of the first infection toward older ages is an indirect effect that may be unfavourable if the infection later in life causes more serious disease (4). This is a particular problem with rubella, which has its most severe consequences in the first trimester of pregnancy (5). Another example is a vaccine-induced pneumococcal serotype replacement in which the vaccine-serotypes may be replaced with more invasive non-vaccine serotypes as causes of nasopharyngeal carriage and disease (6-8).

Transmission models have been used to investigate the underlying dynamics of infectious diseases and to predict the overall effectiveness of vaccination programmes (8, 21). These models have been utilised increasingly in cost-effectiveness evaluations of vaccination programmes (22, 23).

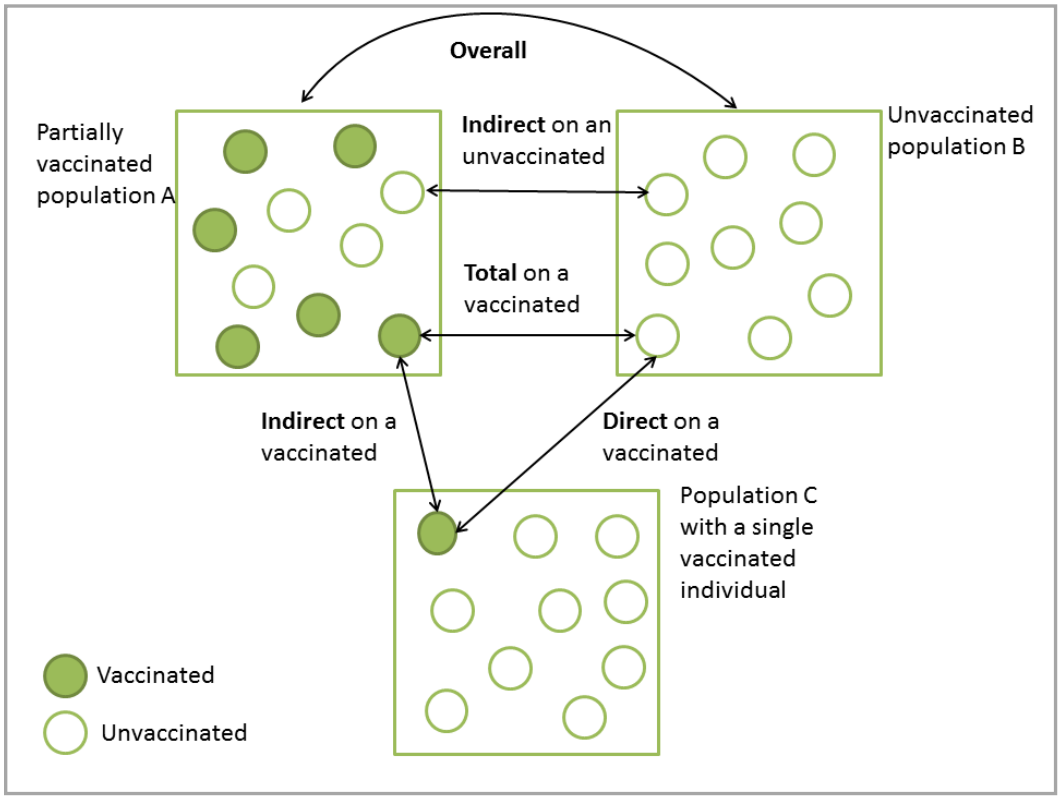

Figure 2. Conceptualisation of different vaccination effects in vaccinated individuals, unvaccinated individuals, or in the whole population.

3.3 Economic evaluation of the pneumococcal conjugate vaccination programme

3.3.1 *Streptococcus pneumoniae* and pneumococcal diseases

Streptococcus pneumoniae, or pneumococcus, is a bacterial species that consists of more than 90 immunologically distinct serotypes. These serotypes are further grouped into 46 serogroups, based on immunological similarities (24). Pneumococcus enters humans through the respiratory tract and can remain on the nasopharyngeal surfaces without causing symptoms (25). Pneumococci residing in the nasopharynx of children are the reservoir for the spread of species between people. Occasionally the pneumococcus proceeds from the nasopharynx and invades normally sterile sites or body fluids, causing disease.

The spectrum of pneumococcal diseases is wide. The invasive pneumococcal diseases (IPD), such as meningitis, bacteraemia and bacteraemic pneumonia, occur most commonly in children <2 years of age and in older people. The pre-vaccination IPD incidence per 100 000 person-years in children <2 years of age has been close to 200 in the USA (26), and 50–60 in the UK (27) and Finland (28). In older people (≥65y), the corresponding rates have been around 60 in the USA, 35 in the UK, and 30 in Finland. The variation in the reported IPD incidence in young children between Western Europe and North America has been well-known and is usually explained by more frequent blood-culture practices in the USA, notably in less severe bacteraemia cases (29). Thus, less severe IPD cases may be under-detected in Europe.

Increasing age, race, chronic medical conditions, conditions causing immunodeficiency as well as socioeconomic environmental and behavioural factors are known risk factors for pneumococcal diseases. Different proportions of these populations at risk affect national differences in the incidence of pneumococcal diseases. The non-invasive infections (pneumonia, sinusitis, mastoiditis, acute otitis media) are typically less severe but more common manifestations of pneumococcal infection (30-32). The national differences in the incidence of the non-invasive diseases may be due to differences in case definition, study designs, diagnostic procedures, and management of the disease, for example, in antibiotic prescribing practices. The clinical diagnosis has varied between countries and studies. In addition, because the causative pathogen of non-invasive infections is rarely identified, the etiological diagnosis often remains unclear.

Community-acquired pneumonia (CAP) causes a significant burden of disease. As in IPD, the incidence of CAP is highest among young children and older people and varies greatly by study and country (30, 33). A Finnish study (34) has reported the highest annual age-specific pre-vaccination incidence rate (per 1000 person-years) of CAP in children aged <5 years (36.0) and in older people aged ≥75 years (34.2). As expected, the lowest incidence was reported in the population aged 15–74 years (8.8). In two population-based Finnish studies, the annual pre-vaccination incidence rate per 1000 person-years of hospital-diagnosed

pneumonia was 13.3 for children aged <5 years (35) and of CAP 15.8 for older people aged ≥65 years (36). In Finland, 37% of bacterial CAP was potentially due to pneumococcus in hospitalised children in 1993–1995 (37) and 17% in radiologically confirmed CAP in older people in 2005–2007 (36).

Elsewhere in Europe, CAP incidence has varied from around 3 (38) to 14 (39) per 1000 person-years among older people. In the UK (40) and Norway (41), CAP incidence was around 3 per 1000 person-years in children aged <5 years.

Acute otitis media (AOM) is one of the most common infections affecting infants and young children, and one of the main reasons for antibiotic treatment (42, 43). The incidence of AOM has varied greatly between studies. The pre-vaccination incidence of acute otitis media among children aged <2 years was reported to be 1.24 episodes per person-year in a prospective, randomised, double-blind cohort study from Finland (44) and 0.282 episodes per person-year in a retrospective cohort study from the Netherlands (45). In a prospective birth cohort study from Germany, during the first 2 years of life, a child had on average 2.2 episodes of AOM and during the first 12 months of life on average 50.6% of children with AOM were treated with antibiotics (46).

3.3.2 Pneumococcal conjugate vaccines and the effectiveness of the vaccination programme

Vaccines

The first pneumococcal vaccine, the polysaccharide vaccine (PPV), was licensed in the late 1970s. In adults PPV has shown to effectively prevent IPD and has been associated with some reductions in non-bacteraemic pneumonia but not in upper respiratory tract infections (47, 48). PPV has not been shown to be effective in children aged <2 years.

To improve the immune response to the capsular polysaccharide in young children, novel vaccines in which capsular polysaccharides are conjugated to one of several different proteins were developed and tested (49). The first pneumococcal conjugate vaccine (PCV), containing 7 serotypes of Streptococcus pneumoniae (Prevenar®) was licensed in the USA in 2000. A year later (2001) it was granted a central marketing authorisation by the European Commission in 2001. PCV7 contains capsular polysaccharide antigens of seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F).

PCV7 was first introduced in the US NVP in 2000 (50). Afterwards, it has been widely introduced in vaccination programmes, for example, in Australia (2005), Canada (2005), the UK, the Netherlands, and Norway (2006), Belgium (2007), and Sweden (2009) (51). PCVs containing 10 (Synflorix®) and 13 (Prevenar 13®) serotypes of Streptococcus pneumoniae were granted a central marketing authorisation in 2009 (52, 53). Since that time, PCV7 has been replaced by PCV10 or PCV13. In Finland PCV was included in the NVP in 2010 in the form of PCV10.

PCV efficacy and effectiveness trials

The efficacy of PCV7 against IPD was first shown in the Northern California Kaiser Permanente (NCKP) efficacy trial. The vaccine efficacy of PCV7 against vaccine-serotype (VT) IPD was reported to be 97.4% in the per-protocol analysis and 93.9% in the intention-to-treat analysis (54). In the intention-to-treat analysis the vaccine efficacy of PCV7 against any IPD was reported to be 89.1% (54), against all clinically diagnosed pneumonia 4.3% (55), and against episodes with a positive radiograph 17.7% (55).

PCV7 has also been shown to reduce otitis media in young children. In the per-protocol analysis, the efficacy of PCV7 against all otitis media episodes was 7.0% in the NCKP trial (54) and 6.0% in the Finnish Otitis Media Vaccine Trial (44).

In a Finnish nationwide cluster-randomised double-blind trial (FinIP), PCV10 total (direct + indirect) effectiveness against culture-confirmed IPD (irrespective of serotype) was reported to be 93% (20) and against suspected IPD (non-laboratory-confirmed) 62% (56). There are no published randomised controlled trial data assessing the clinical efficacy of PCV13 against IPD. However, the vaccine efficacy has been shown in non-inferiority trials by comparing the PCV13 immunogenicity (antibody concentrations) to that of PCV7, which has demonstrated efficacy against pneumococcal diseases (57-59). In addition, PCV13 has been shown to reduce nasopharyngeal colonization of the additional PCV13 serotypes (59).

There are several PCV vaccine efficacy studies, where the gain in reduced risk of VT nasopharyngeal carriage is partly offset by the serotype replacement of NVTs among the vaccinated (60-63). The impact of this replacement in carriage on the incidence of IPD depends on the difference in the invasiveness of the replacing serotypes and replaced serotypes (7, 8).

Impact of PCV in national vaccination programmes

At the population level the indirect effects of the vaccine programme are due to changes in the pneumococcal serotype circulation in the vaccinated population. The risk of VT carriage is further reduced among the vaccinated and unvaccinated. The NVT replacement offsets the gain in reduced risk of VT carriage and disease both in the vaccinated and unvaccinated. Replacement in carriage has been reported in several observational post-licensure PCV7 studies (64-67). Weinberger and colleagues (7) have suggested that since the replacement in disease has not been as complete as in carriage, the invasiveness of the replacing serotypes may be lower. In addition, potential biases in the pre-vaccination carriage data and the disease surveillance systems could underestimate the replacement in disease.

The first post-vaccination year estimates of the effects of the PCV7 programme on IPD incidence rates among the vaccinated and unvaccinated come from the USA. Among the unvaccinated the rate of IPD incidence was reported to decrease by 32% in those aged 20–39 years, 8% in those aged 40–64 years, and 18% in those aged ≥65 years (68). Later post-vaccination surveillance in the USA and Europe has showed that the PCV7 programme has decreased VT IPD in all age groups (6, 27, 69, 70). However, many studies have reported that

the PCV7 programme was associated with increased NVT IPD incidence in all age groups. Among children, the reported overall IPD incidence has still been lower than in the pre-vaccination era (6, 27, 70). In the USA, the overall IPD incidence across all age groups has declined by 45% after the introduction of PCV7 (6). In England the overall reduction in IPD has been 56% among children aged <2 years and 19% in those aged ≥65 years and 34% across all age groups (27).

An observational study comparing the hospitalisation rate for pneumonia in the USA before and after the PCV7 vaccination program was introduced have reported that after a decade the rate of pneumonia hospitalisations declined particularly in children aged <2 years (43.2%) and those aged 85 years and older (22.8%) (71). In the age groups between, the reduction in hospitalisations was reported to range from 4.5% to 13%, except in the 40–64 year olds, whose rate has increased modestly. It is noteworthy that the observational study design ignores other factors that have also been changed over time besides vaccinations and therefore have an additional impact on the results.

In Finland, a population-based observational follow-up study has reported a 48% reduction in IPD incidence among unvaccinated children aged 2–5 years during the first three years after the introduction of PCV10 in the NVP (72). In the UK, PCV7 was introduced into the NVP in 2006 and PCV13 replaced PCV7 in April 2010. The incremental effect of PCV13 versus PCV7 was investigated in a national surveillance study, where the incidence of IPD in the epidemiological year 2013–2014 was compared to the pre-PCV13 baseline (years 2008–2010) in England (73). The reported decline in the IPD incidence was nearly 50% among those aged ≤44 years, 25% among those aged 45–64 years and 25% among those aged 65 and older.

3.3.3 Economic evaluations

When PCV7 was licensed in the USA (2000) and in Europe (2001), it was the most expensive vaccine in the market at the time. In the first European economic evaluations, the assumed price per dose ranged from EUR 40 to EUR 65 (74). Decision-makers considering PCV7 in the public funded NVPs required evidence on the cost-effectiveness of the vaccination programme. Economic evaluations estimating the cost-effectiveness of PCV7 were funded either at least partly by the manufacturer (75-92) or by government, university or foundation (93-102).

In the economic evaluations, the efficacy of the PCV7 vaccination programme among the vaccinated was estimated from the Kaiser Permanente Pneumococcal Conjugate Efficacy Trial (54, 55) and the Finnish Otitis Media Vaccine Trial (44). Yet the effectiveness of the vaccination programmes against IPD has varied between the studies, since in most of the studies the vaccine efficacy has been adjusted to correspond to the country-specific serotype distribution (77-79, 81-84, 86-89, 91, 94-96, 100, 102). In addition, different assumptions for the waning immunity have caused variation.

Only a few economic evaluations of the PCV7 programme have reported an acceptable level of cost-effectiveness either from the societal (79, 80, 82) or health care provider perspective (78, 93), when only direct effects of the programme were taken into account.

The assumptions on herd protection and serotype replacement have been found to be major factors influencing the cost-effectiveness of the PCV7 programmes (74, 103). After the first post-vaccination year, estimates of the effect of the PCV7 vaccination programme on IPD in the USA (68) had demonstrated a considerable reduction in the IPD incidence among both the vaccinated and unvaccinated; hence, vaccine-induced herd protection was included in most economic evaluations of PCV7 (83-92, 96, 100, 101). European studies have used the US post-vaccination estimates of decline in the IPD rate after adjusting it to correspond the country-specific serotype distributions. The US estimates have also been used to evaluate the post-vaccination cost-effectiveness of the PCV7 programme in the USA (85, 90). In addition, observational post-vaccination data of their own have been used in economic evaluations of the PCV7 programme in Quebec, Canada (92) and Australia (104, 105).

The inclusion of herd protection using the US post-vaccination estimates in the economic evaluations has led to a 30–90% reduction in the cost per QALY estimate (83, 84, 86, 88, 96, 100). In fact, these studies have concluded that the PCV7 programme is unlikely to be acceptably cost-effective without the inclusion of herd effect in the analysis. The assumptions on indirect effects are also highly influential regarding the cost-effectiveness of PCV10 and PCV13 programmes (106). The cost of the vaccination programme that have also been found to be highly influential in determining the cost-effectiveness of the PCV7 programme include the price per vaccination schedule (4 or 3 doses) and the administration costs.

Economic evaluations using observational post-vaccination data were reported to be acceptably cost-effective (92) or even cost saving (90) from the health care perspective in Canada and the USA. Newall and colleagues (104) have reported that the PCV7 programme is unlikely to have a cost-effectiveness ratio below a conventional acceptability threshold in Australia at the initial vaccine price. However, if the observed reduction in CAP deaths in Australia was assigned to the PCV7 programme the programme was reported to be cost-effective.

3.4 Economic evaluation of influenza vaccination programme for healthy children

3.4.1 Influenza and influenza-related diseases in children

Influenza virus types A and B cause an extensive burden of illness in children (107-109). Annually recurring epidemics vary in timing and circulating subtypes (110). The severity of disease varies from mild to severe infections requiring health care services. Assessment of the burden of influenza is not straightforward as the symptoms are non-specific and patients with symptoms are not routinely tested for the causing pathogen. The clinical diagnosis of influenza has shown to be inaccurate, especially in small children (111, 112).

In a Finnish cohort study, the attack rates of influenza illness among children with any sign of respiratory infection were reported to be 17.9 for children aged <3 years old, 17.5 for children aged 3–6 years old, and 14.2 for children aged 7–13 years old (108). In a meta-analysis and economic evaluation that used the attack rates derived from placebo arms of vaccine efficacy trials, the attack rate of influenza was reported to be 15.20% for children aged <18 years (113) and 19.21 for children aged <12 years (114). The Houston Family Study has reported a high attack rate (33.0%) for infants aged <1 years (115).

In a study that estimated the influenza-related proportion of health care outcomes of acute respiratory illness episodes in England, the influenza-related hospital admission rate was reported to be highest (1.9 per 1000) in children aged <5 years (109). In a prospective cohort study, the annual rate of hospitalisations due to influenza was reported to be 2.3 per 1000 children aged <5 years (107).

According to a Finnish cohort study, AOM was diagnosed in 39.7% of the children aged <3 years old and was reported to be the most frequent complication of influenza in all age groups. In a retrospective study of children treated at Turku University Hospital (Finland) among children with influenza A (median age 2.0 years), otitis media was developed in 26% and pneumonia in 9% of the children and among those with influenza B (median age 4.2) otitis media was developed in 19% and pneumonia in 8% of the children (116).

3.4.2 Influenza vaccines and effectiveness of the vaccination programme in children

The influenza vaccine protects against highly contagious influenza virus and is given annually. Inactivated influenza vaccine has been accessible since the 1940s and is authorised for anyone six months of age and older (110). Live attenuated influenza vaccines (LAIV) were licensed in the United States in 2003 (110) and in Europe 2011 (117) where it is authorised for persons aged 2–17 years. Inactivated vaccine is administered via intramuscular injection and LAIV is administered via nasal spray (110).

Trivalent inactivated influenza vaccine (TIV) contains three different influenza subtypes: two influenza A subtypes and one influenza B subtype. Quadrivalent inactivated influenza vaccine contains an additional influenza B subtype and is gradually becoming available in Europe (117). Also quadrivalent LAIV4 has been available from season 2014–2015.

Predicting the effectiveness of an influenza vaccination programme is complicated and using the vaccine efficacy estimates directly from clinical trials is problematic (118). In clinical trials, the efficacy of TIV in children has been reported as varying from no efficacy (119) to over 80% (120, 121). The wide variation is largely explained by seasonal variations in the influenza incidence and the match between the vaccine and circulating subtypes of the virus (118, 122). In the clinical trials performed during seasons with a good vaccine match, the effectiveness of TIV has been 50 to 80%, whereas studies with a poor or suboptimal match have reported lower estimates of vaccine effectiveness (122). According to clinical trials the effectiveness of LAIV is better than the effectiveness of TIV. In a meta-analysis of nine randomised clinical trials the efficacy of LAIV when compared to placebo was reported to be 72% against any subtype of influenza virus (123). A large trial comparing LAIV and TIV in children aged 6–59 months has reported 55% higher relative efficacy of LAIV compared with TIV (124).

There are also other factors that make predicting the impact of vaccination programme difficult. Accuracy in case ascertainment varies between clinical trials due to differences in endpoints, clinical diagnosis and virological testing (118). In addition, the indirect (herd) effect of the vaccination programme may substantially increase the overall effectiveness of the vaccination programme (125). The importance of children as transmitters of the influenza infection has been shown in clinical trials (126-128). The potential in preventing influenza in the entire population by vaccinating children has received increased attention. Several dynamic models constructed to investigate the transmission of influenza infection in the population and the effect of vaccinations has shown that targeting vaccinations in children effectively prevents influenza in the entire population (129-131).

3.4.3 Economic evaluations

Economic evaluations of influenza vaccinations in healthy children have been performed for TIV (114, 130, 132-142), for LAIV (143-145), and for both vaccines (146-148). Only a few studies have estimated the incremental cost-effectiveness of LAIV compared to TIV (149, 150). The cost-effectiveness was assessed in different age groups. In some studies, the cost effectiveness was investigated only in small children. In these studies the cost-effectiveness was investigated in children whose ages ranged from 6 months to 2–5 years (136, 137, 144, 146) or in children whose ages ranged from 15–24 months to 5–6 years (134, 143, 149). In other studies, school children and teenager were also included in the analyses. In these studies the cost-effectiveness was investigated in children whose ages ranged from 6 months to 13–18 years (130, 133, 135, 147) or from 2–5 years to 14–18 years (138-140, 145, 148, 150).

Some of the studies reported TIV vaccinations to be cost-saving from a societal perspective but acceptably cost-effective from a health care provider perspective (132, 137-140). For example, in economic evaluations of TIV in children aged 6–60 months (137), in children aged 3–14 years (138), and in children aged 5–17 years (140), the ICER of the programme was reported to be under EUR 15 000 per QALY gained from the health care provider perspective. Prosser and colleagues (147) have reported that the cost-effectiveness of TIV decreases with age. The ICER was reported to be ≤USD 28 000 in children younger than 5 years old and USD 79 000 in children aged 5–11 years. The ICER of the LAIV vaccination programme in children aged 12–18 years was reported to be under EUR 1000 per QALY gained from the health care provider perspective. From the health care provider perspective, TIV vaccinations were reported to be cost-saving in children aged 6–59 months (146) and in children aged 6 months to 13 years (135).

The economic evaluations vary substantially due to many choices concerning methodological and modelling issues that apparently affect the cost-effectiveness estimates of the vaccinations. The inclusion of a societal perspective (e.g. productivity costs due to parental work absenteeism because of taking care of the sick child) has improved the cost-effectiveness ratio of the vaccinations in the studies. Some studies counterbalanced the productivity costs by costs of taking the child to the vaccination visit (132, 134-137, 143, 145-147, 150). Likewise, including the indirect protection of non-vaccinated age groups were found to improve the cost-effectiveness ratio. Only a few economic evaluations have been based on a dynamic transmission model (130, 140, 148) and some have included an indirect herd effect in their static model by reducing the secondary attack rate of influenza among household members of vaccinated children (132, 134, 136, 137, 139, 144-146, 149, 150). A static model, even if taking into account the secondary cases in the families of the vaccinated children, is likely to underestimate the benefits of the vaccination programme.

3.5 Economic evaluation of HPV vaccination programme

3.5.1 HPV infection and HPV related diseases

Cervical human papillomavirus (HPV) infection is a common sexually transmitted infection. A recent meta-analysis of 1 million women with normal cytological findings has estimated the global HPV prevalence to be approximately 12% (151, 152). HPV prevalence is known to vary by age and geographical region. The prevalence has been reported to be highest in Sub-Saharan Africa (24.0%), Eastern Europe (21.4%) and Latin America (16.1%) and lowest in Western Asia (1.7%). In Northern Europe, the prevalence has been reported to be 10%. In all regions, the first HPV peak prevalence has been reported to occur in women under the age of 25 years (152). In Finland, the HPV prevalence rate was reported to be 7.5% among women aged 25–65 years attending the organised cervical screening and 24.1% among women aged 25–29 years (153). In young women, when the infection is most prevalent, about 90% of the HPV infections clear within two years (154).

The link between HPV and cervical cancer was shown in the 1980s (155). HPV is considered a necessary but not sufficient factor for the development of cervical cancer (156, 157). In addition, HPV is also known to cause a substantial proportion of anus, penis, vagina, vulva and head and neck cancers (158, 159).

More than 100 HPV types have been identified, 40 of them cause infections in the genital tract (160). High-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82) are associated with invasive cervical cancer. Persistent high-risk HPV infection may lead to cervical intraepithelial neoplasia (CIN1–3) and progress further to invasive cancer (161). HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases (156, 162) and about 50% of CIN 2/3 (163).

The incidence of cervical cancer is known to vary widely by region. Arbyn and colleagues (164) have reported the rates estimated from the GLOBOCAN 2008 database that provides estimates of the incidence from common cancer types for 184 countries of the world. The highest age-standardised cervical cancer incidence rates are in Eastern, Southern and Western Africa (>50/100 000) and the lowest in Western or South-Central Asia e. g. Gaza and West bank (<1/100000). In Europe, the lowest age-standardised incidence rates are in Malta, Finland, Greece, and Switzerland (≤4.0/100 000).

Screening has had a considerable impact on the incidence of cervical cancer (165, 166). The CIN cases are effectively found by the screening system. Therefore, the detected number of CIN cases reflects the screening practice of the country in addition to the disease burden.

3.5.2 Primary and secondary prevention of cervical cancer

Secondary prevention of cervical cancer was introduced in the 1960s in Finland (167). Cervical cancer screening has been based on the cytological Pap (Papanicolaou) test. Organised, population-level cytological screening can reduce the incidence of cervical cancer by up to 80% (165). According to the European Union recommendation, cancer screening should only be performed in population-based, organised screening programmes.

Primary prevention against cervical cancer has been available since 2006. Bivalent (types 16 and 18) and quadrivalent (types 6, 11, 16, and 18) HPV vaccines prevent HPV types that cause the most cervical cancers and a portion of the cancers of the anus, vulva, vagina, penis and oropharynx (168-170). The quadrivalent vaccine prevents, in addition, HPV types that cause most genital warts. The 9-valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) was granted marketing authorisation in Europe in June 2015 (171).

The first group of countries to introduce the HPV vaccination into national immunization programmes in 2006–2007 were e. g. USA, Belgium, UK, Australia, and Canada. By the end of 2012, the HPV vaccination had been introduced into the NVP already in more than 40 countries (172, 173). All Nordic countries have included HPV vaccination in the NVP: Norway and Denmark in 2009, Iceland in 2011, Sweden in 2012, and Finland in 2013.

Both bivalent and quadrivalent vaccines have demonstrated high efficacy against vaccine type HPV infection (169, 174, 175). In addition, both vaccines have shown cross-protection against non-vaccine HPV types (176, 177). In a meta-analysis, the bivalent vaccine was reported to have better cross-protection against non-vaccine HPV types 31, 33, and 45 than the quadrivalent vaccine (178). However, the differences were not all significant and the results might suggest waning cross-protection. An indirect herd effect has been shown in Australia, where the HPV vaccination programme for all women aged 12–26 years have decreased the genital warts incidence both in vaccinated women and non-vaccinated heterosexual men (179).

3.5.3 Economic evaluations

The early economic evaluations of HPV vaccination programmes targeting adolescence girls were based on static cohort models and therefore were unable to explore the indirect herd effect of the vaccination programme (180-182). Recent economic evaluations are based on both static models and dynamic transmission models.

In the Netherlands the HPV vaccination programme was assessed to be acceptably cost-effective (EUR 19 430 per QALY gained) by Coupé and colleagues (183) but not cost-effective (EUR 53 500 per QALY gained) by de Kok and colleagues (184), with a Dutch willingness to pay threshold of EUR 20 000 per QALY. The main reason for the difference in results in these two studies was in the used discount rates. Coupé and colleagues used a 4% discount rate for costs and 1.5% for effects according to the national guidelines, while de Kok

and colleagues used a 3% discount rate for both costs and effects. Both analyses were based on a static cohort model. In an analysis that was based on a transmission dynamic model, the HPV vaccination programme was reported to be cost effective (GBP 22 500 per QALY gained) at a willingness to pay threshold of GBP 30 000 per QALY gained in the UK (185). In a static model, the cost-effectiveness ratio was estimated to be CAD 31 000 for bivalent vaccine and CAD 21 000 quadrivalent vaccine per QALY-gained in Canada (186).

According to several reviews, vaccinating girls against HPV before their sexual debut is likely to be cost-effective (187-189). The duration of vaccine-induced protection, vaccination costs, and discount rate were among the parameters that were most influential on the results of the economic evaluations.

4 Materials and methods

In this study, we conducted economic evaluations of the infant 7-valent pneumococcal conjugate vaccination programme (I) and childhood influenza vaccination programme (II), and also a burden of disease analysis of HPV-related genital diseases in women (III, IV).

The incidence of the pneumococcal, influenza and HPV-related disease outcomes and the disease-related health care resource use were estimated from register data and epidemiological studies.

The economic evaluations in articles I and II were based on a static cohort model where only the effect of the vaccination programme on the vaccinated was included in the analyses. In order to investigate the impact of indirect effects on the cost-effectiveness of the infant PCV7 vaccination programme among the unvaccinated, an economic re-evaluation by means of a static model was conducted in 2008 (PCV7-II) when PCV7 was reconsidered to be included into the NVP. The methods and results of the unpublished economic re-evaluation of the PCV7 vaccination programme (PCV7-II) are also presented here. *In this thesis, the first evaluation is referred to as PCV7-I (published in article I) and the second as PCV7-II (previously unpublished)*.

4.1 Models

The models used in the economic evaluations and the overview of the studies are shown in Table 1. In the economic evaluations of the PCV7 vaccination programme, unvaccinated and vaccinated hypothetical birth cohorts were followed from birth until 5 years (PCV7-I) or 100 years (PCV7-II) of age in a Markov cohort model. The transition probabilities between Markov states were estimated from annual, age-specific incidence rates for pneumococcal disease outcomes in Finland. In the first study (PCV7-I) the health states of the Markov model were pneumococcal meningitis, pneumococcal bacteraemia, community-acquired pneumonia (CAP), acute otitis media (AOM), death, and no pneumococcal disease. In the second study (PCV7-II) the health states were pneumococcal meningitis, pneumococcal bacteraemia, pneumonia treated in secondary health care, pneumonia treated in primary health care, AOM, pneumococcal death, death from other causes, no pneumococcal disease.

Table 1. Model and study design

	PCV7-I	PCV7-II	Influenza	HPV
Publication year	2005 (I)	Previously unpublished	2006 (II)	2013 (III), 2014 (IV)
Study type	CEA, CUA, CBA	CUA, CEA	CEA	Cost of illness, retrospective
Perspective	Health care, societal	Health care	Health care, societal	Health care
Discount rate[1]	3 %	5 %	N/A	N/A
Price level[1]	2004	2007	2004	2010
Model	Markov cohort model	Markov cohort model, Static population model	Decision analysis model	N/A
Effect on the vaccinated	Yes	Yes	Yes	N/A
Effect on the unvaccinated	No	Yes	No	N/A
Time horizon, years	5	100	1 (one season)	1
Duration of direct protection, years	5	5	1	N/A
Vaccine coverage (%)	100 %	97 %	100 %	N/A
Vaccine schedule	4 doses	3 doses	first year 2 doses, subsequent years 1 dose	N/A
Vaccine price (EUR) per dose[1]	50.5	48	2.3	N/A
The outcome of the analysis	LYG, QALYs gained	LYG, QALYs gained	Outcomes and costs prevented,	Number of cases, health care costs
Size of population followed	57 574	58 000	56 000	N/A

N/A, not applicable
[1]in the original publication (I, II, III, IV) or original study (PCV7-II)

In both cost-effectiveness analyses of the PCV7 programme, (PCV7-I, PCV7-II) the direct effect of the vaccination was assumed to last for 5 years. In the second evaluation reassessing the cost-effectiveness of the PCV7 programme, the indirect herd effect of the vaccination programme (herd effect and serotype replacement) was incorporated, assuming the reduction in the pneumococcal disease outcomes over the unvaccinated population (≥5 years of age) to occur when a steady state has been reached after the initiation of the programme. Thus, an external indirect herd effect factor was applied in the static cohort model. In the model, the indirect herd effect was assumed to occur annually for a steady-state population. The model was run in monthly cycles for the first 6 years and in annual cycles for the following 94 years.

In the economic evaluation of childhood influenza vaccination programme, unvaccinated and vaccinated hypothetical annual age cohorts aged from 6 months to 13 years were compared in a decision analysis model. The model considered the following disease outcomes: uncomplicated influenza, influenza with AOM, influenza with sinusitis, influenza with pneumonia (treated as outpatients), severe influenza (treated in secondary health care). In the model, all influenza- and vaccination-related costs and benefits took place during the concurrent influenza season. Only cases that received medical attention were included in the analyses.

In order to assess the total burden and health care provider costs of prevention, management, and treatment of female HPV-related genital disease outcomes in Finland, we conducted a cost of illness study. This retrospective population-based registry study included all organised and opportunistic screening tests.

4.2 Burden and costs of potentially vaccine-preventable diseases

In order to estimate the incidence of pneumococcal-, influenza- and HPV-related disease outcomes as well as the health care resources used for the management and treatment of the disease outcomes, we established datasets as shown in Table 2. The datasets contain data from nationwide or regional population-based registers, epidemiological studies, and one vaccine efficacy trial. The population-based register data were extracted by identifying the individuals and the health care resource use for the disease in question.

In Finland, individual-level administrative register data are available that are linkable using the unique personal identity code. The personal identity code remains unchanged throughout the person's lifetime and is used for identification in practically all administrative registers in Finland. The individual-level register data were retrieved either with an encrypted personal identity code (PCV7-I, PCV7-II, II) or with the unique personal identity code (III, IV).

In the encrypted data, the identity code was encrypted within each register, hence, we were able to identify each individual's events within each register (provider) but not between the registers (providers). Thus, we were not able to identify the whole treatment episode for an individual. For example, a patient that has first contacted primary care may be referred to secondary care during the illness. Double counting the individual from the unlinked registers was avoided by using one data source (e. g. IPD, influenza) or using an epidemiological study (pneumonia) when estimating the incidence of disease outcomes from register data. The dataset containing the unique personal identity code itself (III, IV) provided information for categorising the individuals according to the most severe HPV-related disease outcome by linking each individual's events within and between the different registers.

4.2.1 Epidemiological data

From the population-based register data we identified all individuals who had at least one outcome related to the disease outcome in question recorded in the appropriate health register. The case definitions were as specific as possible from the data available. The incidence of disease outcomes that were estimated from the register data were assessed by dividing the outcome cases by age-specific population estimates for Finland (Official Statistics of Finland, OSF) for the corresponding time period. The age-specific background mortality rate was obtained from Causes of Death statistics (OSF).

The influenza data source differed most from the others. The incidences of influenza and its complications (II) were obtained from an epidemiological study (108). The cases were laboratory confirmed but uncertainty lies in the seasonal variability of influenza epidemics. On the other hand, all incidences of HPV-related disease outcomes (III) were estimated from nationwide population-based register data. In the economic evaluations of the PCV7 programme, the incidences of IPD and otosurgical procedures (PCV7-I, PCV7-II) and the incidence of pneumonia in secondary health care (PCV7-II) were estimated from nationwide population-based register data. The incidence of pneumonia in the first PCV7 evaluation (PCV7-I) were obtained from an epidemiological study and the incidence of AOM (PCV7-I, PCV7-II) was obtained from a vaccine efficacy trial. The incidence of pneumonia in primary health care (PCV7-II) was estimated using several data sources.

Table 2. Burden of disease datasets, epidemiological data

	PCV7-I	PCV7-II	Influenza	HPV
Publication year	2005 (I)	Unpublished	2006 (II)	2013 (III), 2014 (IV)
Target population, age	0–4y	All ages	6m–13y	Females 15+y
Registers (individual-level data)				
Data linkable between registers	No	No	No	Yes
Data linkable within register	Yes	Yes	Yes	Yes
Health Care Register[1, 3]	1996–1999	2000–2006	N/A	1999–2008
National Infectious Disease Register[3]	1995–2000	2000–2006	N/A	N/A
Finnish Cancer Registry[3]	N/A	N/A	N/A	1990–2008
Mass Screening Registry[3]	N/A	N/A	N/A	1999–2008
SII[2] Register of Special Reimbursements for Medical Expenses[3]	1996–1999	2000–2005	N/A	1999–2008
SII[2] Register of Prescribed Medicines[3]	N/A	N/A	N/A	2004–2008
Register of the Finnish Student Health Service[3]	N/A	N/A	N/A	1999–2008
HUSLAB Pathology Laboratory Register[4]	N/A	N/A	N/A	2004–2008
Primary health care data[4]	N/A	2001–2006	N/A	N/A
Turku University Hospital Register, hospital emergency department visits[4]	N/A	N/A	1988–2004	N/A
Registers (aggregated data)				
Cause of Death Statistics, OSF[3]	1997–2001	1996–2005	1997–2002	1990–2008
Life expectancy, Population and Cause of Death Statistics, OSF[3]	Yes	Yes	Yes	Yes
Epidemiological studies				
FinOM vaccine trial[5] (44)	Yes	Yes	N/A	N/A
Incidence of AOM in Western Finland[6] (190)	Yes	Yes	N/A	N/A
Aetiology of paediatric CAP in Eastern Finland[6] (191)	Yes	Yes	N/A	N/A
Incidence and outcome of IPD in Finland 1995-2002[3, 7] (192, 193)	Yes	Yes	N/A	N/A
Respiratory infections in children aged 0–13 years[6] (108)	N/A	N/A	Yes	N/A

N/A, not applicable
[1] former Hospital Discharge Register
[2]Social Insurance Institution
[3] Nationwide data
[4] Regional data
[5] Randomised, double-blind cohort study
[6] Cohort study
[7]A population-based registry study

4.2.1.1 Pneumococcal disease outcomes (PCV7-I, PCV7-II)

The incidence of invasive pneumococcal disease (IPD) was estimated from laboratory-confirmed cases retrieved from the National Infectious Disease Register. Data from six-year periods 1995–2000 and 2000–2006 were used for the first (PCV7-I) and second (PCV7-II, Table 3) evaluations, respectively. In both evaluations, the case fatality ratio for IPD was obtained from a Finnish population-based registry study linking the laboratory-confirmed IPD cases from the National Infectious Disease Register to their vital status in the National Population Information System (192). The case fatality ratio was 1.2%, 9.7%, 14.5% and 22.9% for IPD cases aged <18 years, 18–49 years, 50–74 years and aged ≥75 years, respectively.

In the first economic evaluation study of the PCV7 programme in children (PCV7-I), the annual incidence of potentially pneumococcal pneumonia was obtained from a prospective epidemiological study assessing the incidence and aetiology of CAP pneumonia in Eastern Finland (191). According to the Jokinen study (191), the all-cause definite pneumonia incidence per 1000 children aged 0 to 4 years was 14.5 for inpatient treated pneumonia and 13.9 for outpatient treated pneumonia (PCV7-I). In the study reassessing the cost-effectiveness of the PCV7 programme (PCV7-II), we estimated the incidence of potentially pneumococcal pneumonia separately in secondary health care (inpatient and outpatient cases) and primary health care (outpatient cases). The number of pneumonia cases in secondary health care was extracted from the Hospital Discharge Register (2001–2006) with one of the following International Classification of Diseases 10th revision (ICD-10) codes for pneumonia codes as the first-listed diagnosis:

- J13 Pneumonia due to Streptococcus pneumoniae,
- J15.9 Bacterial pneumonia, unspecified,
- J18.1 Lobar pneumonia, unspecified,
- J18.8 Other pneumonia, organism unspecified,
- J18.9 Pneumonia, unspecified

The total incidence of potentially pneumococcal pneumonia in outpatient care was estimated by adding the age group -specific proportion of outpatient cases (191) to the incidence of inpatient cases in secondary health care estimated from the Hospital Discharge Register. The outpatient cases in primary health care were the difference between total outpatient cases and outpatient cases in secondary health care. The total outpatient cases in primary health care were further divided into age subgroups by the data retrieved from two health centres in Southern Finland (Tuusula 2001–2006 and Kangasala 2000–2006).

In the base-case, deaths from pneumonia were not included in the analysis in the first economic evaluation of the PCV7 programme (PCV7-I) and in cases aged 0–19 years in the second (PCV7-II) evaluation. In cases aged ≥20 years, the case fatality ratio for inpatient pneumococcal pneumonia was estimated from the Causes of Death statistics with ICD-10 codes J13 and J18.1 (OSF, 1996–2005). The case fatality ratio increased from 0.04% to 1.3% among cases aged ≥20 years (PCV7-II).

In both economic evaluations of the PCV7 programme, the incidence of AOM was estimated identically and only for children aged <5 year olds. In children aged 0 to 1 year olds, the incidence of all-cause AOM was taken from the Finnish Otitis Media (FinOM) Vaccine Trial (44). The incidence of 2-year-olds was calculated by assuming the incidence of 1-year-olds in the FinOM trial decreased by the same proportion as in a previous epidemiological study of AOM incidence in Finland (190) and the AOM incidences for children aged 3 to 4 years were calculated accordingly.

The incidence of otological surgery procedures due to AOM was estimated from national population-based registry data covering procedures performed in public (Hospital Discharge Register) and private (Social Insurance Institution Register of Special Reimbursements) health care. We included in the analysis both tympanostomies and/or adenotomies (1996–1999) in the first (PCV7-I) economic evaluation of the PCV7 programme and tympanostomies only (2000–2005) in the economic re-evaluation (PCV7-II).

Table 3. Estimated annual incidence and case fatality rate (CFR) of pneumococcal (Pnc)-related disease outcomes in Finland in the economic re-evaluation of the PCV7 programme (PCV7-II)

Age group	Incidence rate[1]						Case fatality rate (%)	
	All-cause AOM	Oto-surgical procedure	Potentially Pnc pneumonia		IPD		IPD	Pnc pneumonia
			Primary health care	Secondary health care	Bacteraemia	Meningitis		
<1	1.004	24.7	1.4	4.8	38.4	4.0	1.7	
1	1.221	67.4	7.4	9.3	72.0	1.8	1.6	
2–4	0.715	27.4	4.4	5.1	19.0	0.2	1.0	
5–9			3.3	2.1	3.5	0.2	0.6[2]	
10–19			2.4	1.3	2.1	0.1	0.6[2]	
20–34			1.3	1.3	5.1	0.2	6.0	0.1
35–49			1.9	1.9	10.4	0.6	11.5	0.7
50–64			1.9	3.4	16.1	0.8	13.9	0.7
65–74			3.4	8.0	21.4	0.5	15.4	0.4
75–84			4.8	16.4	31.7	0.3	22.9[3]	0.5
85+			10.4	27.8	47.9	1.0	22.9[3]	1.0

Estimates in this table are presented in broader age groups. In the analysis, estimates varied by 1-year age bands.

[1]AOM: per person-year, otosurgical procedure, pneumonia: per 1000 person-years, IPD: per 100 000 person-years

[2] Estimate for the 5–17 year olds

[3] Estimate for the ≥75 year olds

4.2.1.2 Influenza-related disease outcomes in children (II)

The incidence of influenza and influenza associated complications (pneumonia, sinusitis, AOM) were obtained from a prospective epidemiological cohort study of laboratory-confirmed respiratory infections in children aged <14 years covering two influenza seasons (108). The influenza incidence per 1000 children was 179 for children aged <3 years old, 175 for children aged 3–6 years old and 142 for children aged 7–13 years old. In corresponding age groups, AOM was diagnosed in 39.7%, 19.6% and 4.4% of the children and sinusitis in 0.8%, 6.8% and 8.8% of the children with influenza, respectively. In addition, a severe illness case was defined as a laboratory-confirmed influenza case seeking care in the hospital emergency department (Turku University Hospital register, 1988–2004). A severe case was defined to be 2.3%, 1.3% 0.3% of the influenza cases in children aged 6 months to <1 years, aged 1–2 years and ≥3 years, respectively. We assumed no influenza-associated deaths to occur in children.

4.2.1.3 HPV-related genital disease outcomes in women (III, IV)

The incidences of cervical, vaginal, and vulvar cancer were estimated from the cancer notifications from the Finnish Cancer Registry (1999–2008). The incidences of adenocarcinoma in situ (AIS) and cervical intraepithelial neoplasia grade 3 (CIN3) were estimated from the Cancer Registry and Hospital Discharge Register data (2004–2008). Other cervical, vaginal, and vulvar intraepithelial neoplasia (CIN1–2, VaIN1–3, VIN1–3) cases were estimated from the Hospital Discharge Register data (2004–2008). The incidence of cases defined as minor cytological abnormalities were estimated using the Mass Screening Registry, the Hospital Discharge Register, the SII (Social Insurance Institution) register on Special Reimbursements, the Student Health Service Register, and the HUSLAB Pathology Laboratory Register (2004–2008). The incidence of external genital warts was estimated from the reimbursed prescriptions of podophyllotoxin or imiquimod in the SII Register of Prescribed Medicines (2004–2008). Imiquimod is also used for other dermatology diseases, mostly among older people. The age-specific pattern of podophyllotoxin and imiquimod use was similar in those aged <45 years. In older age groups, the imiquimod use started once more to increase while podophyllotoxin use continued to decrease. We extrapolated the prescriptions for imiquimod for external genital warts from its other use by applying a similar age-specific pattern of use to that of podophyllotoxin.

4.2.2 Cost analysis

The cost analyses were performed from the health care provider perspective and, in economic evaluations of PCV7 (PCV7-I) and influenza (II) programmes in children, also from the societal perspective. In the first economic evaluation of PCV7 (PCV7-I) in the original publication, the base-case results were shown using the 3% discount rate. However, a 5% discount rate was recommended to be used in Finland when PCV7 was considered for inclusion into the NVP for the first (PCV7-I) and second (PCV7-II) time. Therefore, in this study the base-case results of both economic evaluations of the PCV7 programme are shown using the 5% discount rate for the future benefits and costs. We estimated the average use of health care services and assigned a monetary value (unit cost) to each service. The average health care cost per case included the management and treatment of the disease outcome.

4.2.2.1 Use of health care services

In the economic evaluations of PCV7 (PCV7-I) and influenza (II) vaccination programmes in children, registers, epidemiological studies, international scientific publications and expert interviews were used to assess the health care resource use due to disease outcomes. The assessment was derived from separate sources without using individual-level register data. In the economic re-evaluation of the PCV7 vaccination programme (PCV7-II), the use of health care resources in secondary health care was estimated from individual-level registry data linking each individual's events within the register with the encrypted identity code.

In the cost of illness study of HPV-related genital disease in women (III, IV), the use of health care resources in secondary health care, organised and opportunistic Pap tests by health care provider, and diagnostic and treatment procedures by private provider were estimated from individual-level registry data linking each individual's events within and between the different registers with the unique identity code. Register-based individually linked data provided information that enabled identification of the whole treatment episode per woman and to classify the purpose (screening or follow-up) of the Pap tests taken outside the screening programme. The latter information was essential in estimating the coverage and frequency of Pap testing while taking into account tests taken both within and outside the organised programme.

Pneumococcal-related disease outcomes

The assumed health care resource use due to disease outcomes in the first economic evaluation of the PCV7 vaccination programme (PCV7-I) is shown in Table 4. The health care resource use due to post-meningitic hearing impairment was assessed using expert interviews. The risk of developing a hearing defect after pneumococcal meningitis was assumed to be 32% according to a meta-analysis (194).

Table 4. The average use of health care resources per case due to pneumococcal-related disease outcomes in the first economic evaluation of the PCV7 programme (PCV7-I)

	IPD		Pneumonia		AOM	Otosurgical procedure[1]	References
	Meningitis[2]	Bacteremia	Inpatient	Outpatient			
Inpatient hospitalisation	1	1	1				Expert opinion
Outpatient visits per case							
Primary health care	1	2	2	1	1.45	1	AOM: (195); other outcomes: expert opinion
Secondary health care	2	1	1	1		1	Expert opinion
Courses of antibiotics[3]				1	1		Expert opinion
Outpatient surgery					0.1	1	Health Care Register, SII register

[1]Tympanostomy and/or adenotomy
[2]No complications
[3]in outpatient care

In the economic re-evaluation of the PCV7 vaccination programme (PCV7-II), the average health care resource use in secondary health care due to IPD and pneumonia was estimated from data that included each individual identified with the disease outcome in the Hospital Discharge Register (2000–2006) with the appropriate ICD-10 code. Diagnosis indicating the most serious outcome determined the pneumococcal-related outcome of each case. Pneumococcal meningitis (G00.1) was considered to be the severest outcome, followed by pneumococcal bacteraemia (A40.3), potentially pneumococcal pneumonia (J13, J15.9, J18.1, J18.8, J18.9) being the least severe of these outcome categories. We used the encrypted identity code to identify each individual's events in the register data, while hospitalisations and hospital outpatient visits were extracted with ICD-10 codes related to the pneumococcal disease in question. The health care resource use was estimated for 3 years (meningitis) or one year (other outcomes) after the onset of the disease. The average number of events per case per year was derived by dividing the total number of each event type by the total number of cases in the follow-up.

The risk of sequelae after pneumococcal meningitis and the additional health care resource use due to neurologic sequelae in secondary health care was estimated from Hospital Discharge Register data with appropriate ICD-10 codes. Out of 255 cases of pneumococcal meningitis, 16% had an ICD-10 code referring to neurologic sequelae and 12% to hearing impairment. One in five of the cases that had a hearing impairment likewise had Cochlear implant surgery. Expert interviews were used to evaluate the additional lifetime health care resource use due to hearing impairment.

The average number of physician visits per pneumonia case in primary health care was estimated from data retrieved from two health centres (Tuusula and Kangasala) in Southern Finland. The health care services and medication used due to AOM was obtained from a study that compared the treatment and management of AOM in the FinOM-study and in Porvoo health centre in Southern Finland (196). A case with tympanostomy tube was assumed to visit a physician twice before the otosurgical procedure. In both economic evaluations of PCV7 (PCV7-I, PCV7-II) we assumed that giving one dose of vaccine to a child takes 5 min of a nurse's working time.

Influenza related disease outcomes in children

The average use of health care resources due to influenza was estimated using registers, published studies, and expert interviews (Table 5). Only cases that received medical attention were included in the analyses. The average number of physician visits per case for influenza and its complications was obtained from a prospective epidemiological cohort study of laboratory-confirmed respiratory infections in children (108). In the analysis, we did not vary the estimates for visits per case by age since either the estimates in different age groups were close to each other (AOM in children aged 6 months to <7 years) or there were too few cases to stratify the estimates by age (AOM in children aged ≥7 years and all other complications).

The hospitalization rate for severe illness cases (40%) was derived from virologically confirmed influenza cases in patients who sought medical care in the hospital emergency department in Turku University Hospital during 1988–2004. A follow-up visit was assumed to occur in all pneumonia cases and in 40% of the AOM cases. Bacterial infections were assumed to be treated with antibiotics. We estimated from the first economic evaluation of the PCV7 programme that 0.06 otosurgical procedures were performed per each episode of otitis media in children. The seasonal influenza vaccination is given in the autumn. Thus, unlike PCV7 it is not always given in a regular well-baby clinic visit. Thus, we assumed that giving one dose of influenza vaccine to a child takes 10 min of a nurse's working time. Analogously we did not include in the analysis the pharmacotherapy of symptomatic treatment of influenza nor treating any adverse events related to vaccination.

Table 5. The average use of health care resources per case due to influenza in children aged 6 months to 13 years.

	Influenza with					Reference
	No complications	Pneumonia	AOM	Sinusitis	Severe illness	
Inpatient hospitalisation					0.4	Turku university hospital register
Outpatient visit per case						
Primary health care	1	1.6	1.6	1.4	1	(108)
Secondary health care					1	Turku university hospital register
Follow-up visit		1	0.4			AOM: (196); other outcomes: expert opinion
Courses of antibiotics		1	1.1	1		AOM: (195); other outcomes: expert opinion
Otosurgical procedure			0.06			PCV7-I (I)

HPV-related genital disease outcomes in women

The health-related events due to the management, treatment, and follow-up of the HPV disease outcome in question were extracted from the registers with the appropriate ICD-10 codes (secondary health care), International Classification of Diseases for Oncology codes (cancer register notifications), Nordic Classification of Surgical Procedures codes (diagnostic and treatment procedures), and medical test (Pap test). The diagnosis indicating the most serious outcome determined the HPV-related outcome category of each individual. The HPV outcome categories were ranked in the following declining order of severity: cancer, AIS, CIN3, VaIN3, VIN3, CIN2, VaIN2, VIN2, CIN1, VaIN1, VIN1, minor cytological abnormalities and external genital warts. We used the unique personal identity code to link each individual's (case) health-related events in the different registers. An index event was defined to occur at the time point when a woman was first time assigned the diagnosis that determined its outcome category. At the time point of the index event, the health-related events of each case were divided into 1-year pre- and post-diagnostic periods. We estimated the average number of each events (outpatient visits, inpatient hospitalizations, gynaecological procedures by private providers, follow-up Pap tests) per case by dividing the total number of each event type by the total number of cases in follow-up in the year of interest.

The unique personal identity code was used to link the Pap tests taken within and outside the organised screening with the HPV-related events of a woman. Pap tests were classified by the purpose of the test. A Pap test was taken for screening purposes (screening test) or due to a previous abnormal cytological or histological finding (follow-up test). In the screening programme, both the purpose and the result of the test are registered. For tests taken outside the screening programme, neither purpose nor result of the test is registered except for the test results in the HUSLAB register. A test was considered to be a screening test if it did not fulfil any of the following criteria of a follow-up test:

1. Test taken outside the organised screening within 30 months after an abnormal test in organised screening,
2. Test taken within 15 months after an abnormal test result or within 10 months after a test with unknown result,
3. Test taken within 15 months after a test with an unknown result in the student health service,
4. Test obtained within 30 months after the first-listed diagnosis code or treatment procedure code indicating intraepithelial neoplasia, or at any time after the first cervical, vaginal, or vulvar cancer notification.

We estimated the annual average number of Pap tests as well as the coverage and frequency of Pap testing by age and screening modality in Finland in 2004–8. The numbers of Pap tests were obtained from nationwide data with the exception of the public primary health care (not available) and secondary health care tests (incomplete) that were extrapolated from Helsinki region data. In addition, the Helsinki metropolitan region data were used in estimating the

overall coverage and frequency of Pap testing per woman for the 5-year period of 2004–8. The age of the woman in the coverage and frequency estimations was determined according to the year 2008 (index year). We included in the analyses all Pap tests for each woman that were carried out in 2004–2008 (i.e. during the preceding 5 years of the index year 2008). In assessing the age-specific coverage the denominator was calculated as the mean number of women at the corresponding age in year 2008, one year younger in 2007, two years younger in 2006, and so forth in the Helsinki metropolitan region in 2004–8. With such an average, we corrected the uneven age distribution, especially in young women due to the open cohort, accounting for the positive net migration in young women into the Helsinki region.

4.2.2.2 Health care costs

The sources used in estimating the unit costs is summarised in Table 6 and the main unit cost estimates in the economic evaluations of PCV7 and children's influenza vaccination programmes at the 2010 price level is summarised in Table 7. The unit costs for secondary health care were totally (PCV7-II, III, IV) or partially (II) estimated using individual-level cost accounting data from the Hospital District of Helsinki and Uusimaa in all other studies except the first economic evaluation of the PCV7 programme (PCV7-I). The differences in the unit costs in economic evaluations of PCV7 (PCV7-I, PCV7-II) are due to these different data sources. Other unit cost estimates were mainly taken from the widely used national pricelist for unit costs of health care in Finland (197-199). The unit cost of tympanostomy in private health care was obtained from a price comparison of private health care services (Finnish Consumer Agency 2003). We used retail prices without value-added tax as a cost of pharmacotherapy.

Table 6. Sources used in estimating the unit cost of care. Yes/No indicates whether or not the information was used in the study.

	PCV7-I	**PCV7-II**	**Influenza**	**HPV**
Publication year	2005 (I)	Previously unpublished	2006 (II)	2013 (III), 2014 (IV)
National pricelist for unit costs of health care in Finland	(197, 198)	(199)	(198)	(199)
Primary health care				
Primary care physician visit	Yes	Yes	Yes	Yes
Secondary health care				
Inpatient hospitalisation	Yes	No	No	No
Outpatient visit	Yes	No	Yes	No
Tympanostomy, public health care	Yes	No	No	N/A
Private health care				
Physician visit, specialist	Yes	Yes	No	Yes
Other costs				
The fully-burdened labour cost of a nurse	Yes	Yes	Yes	N/A
Price comparison of private health care services (Finnish Consumer Agency 2003)				
Tympanostomy, private health care	Yes	Yes	Yes	N/A
Individual-level cost accounting data from the Hospital District of Helsinki and Uusimaa				
Secondary health care				
Inpatient hospitalisation	No	Yes	Yes	Yes
Outpatient visit	No	Yes	No	Yes
Tympanostomy, public health care	No	Yes	Yes	N/A

N/A, not applicable

Table 7. The main unit cost estimates in economic evaluations of PCV7 and children's influenza vaccination programmes, euros at the 2010 price level

	PCV7-I (I)	PCV7-II	PCV7-II	Influenza (II)
Target group	**0–4y**	**0–4y**	**5+y**	**0.5–13y**
Secondary health care[1]				
Meningitis, inpatient hospitalisation	8250	7377	11 336	N/A
Meningitis, outpatient visit, emergency department	247	696	896	N/A
Meningitis, outpatient visit	240	194	330	N/A
Neurologic sequelae of meningitis, inpatient hospitalisation	N/A	2983	2710	N/A
Neurologic sequelae of meningitis, outpatient visit, emergency department	N/A	1131	493	N/A
Neurologic sequelae of meningitis, outpatient visit	N/A	287	232	N/A
Bacteraemia, inpatient hospitalisation	2532	1541	6138	N/A
Bacteraemia, outpatient visit, emergency department	247	268	494	N/A
Bacteraemia, outpatient visit	240	176	277	N/A
Pneumonia, inpatient hospitalisation	2085	1548	4968	N/A
Pneumonia, outpatient visit, emergency department	247	198	317	N/A
Pneumonia, outpatient visit	240	159	215	N/A
Influenza, inpatient hospitalization	N/A	N/A	N/A	1868
Outpatient visit, emergency department				253
Tympanostomy, public health care	703	748	N/A	748
Primary health care				
Routine visit to a primary care physician, no tests	71	68	68	70
Primary care physician visit, includes tests, X-ray	71	129	129	125
Visit to speech therapist	61	82	82	N/A
Labour cost per hour, nurse	33	33	33	33
Private health care				
Physician visit, Ear, nose and throat specialist, private health care	77	74	N/A	74
Tympanostomy, private health care	758	800	N/A	800
Costs associated with hearing impairment				N/A
Costs associated with a Cochlear implant, first year	59 501	41 940	37 023	
Costs associated with a Cochlear Implant, subsequent years	734 - 4863	142 - 13442	142 - 11762	
Costs associated with hearing aid, first year	5413	4746	2274	
Costs associated with hearing aid, subsequent years	367 - 4816	107 - 4746	107 - 3067	
Other costs				
Assumed vaccine price (EUR) per dose	60.7	52.3	N/A	2.8
Cost of vaccine administration (EUR) per dose	2.01	2.76	N/A	3.85
Average gross income of Finnish employees per day	208	N/A	N/A	208
Average travel cost per visit in primary health care	6.6	N/A	N/A	6.6

N/A, not applicable

[1]Estimates are presented in broader age groups. In the analysis, estimates varied by 1-year age bands.

In the HPV study (III, IV), the average unit costs in secondary health care (hospitalizations and outpatient visits) were estimated from cost accounting data from the Hospital District of Helsinki and Uusimaa. The estimates included diagnostic and treatment procedures and were estimated for hospitalizations and outpatient visits by outcome and pre- and post-diagnostic periods. The unit cost of a Pap test in the organised screening programme was the mean price of the organised screening test in 5 university towns. The cost included the entire screening package: invitation letter, preparation and interpretation of the test, reply letter, registration, documentation and analysing the screening registry data. In the organised programme the Pap test is carried out by a nurse. Outside the organised programme the Pap test is taken during a physician visit. The cost of a Pap test taken outside the organised programme included the laboratory fees and half (tests with screening purpose) or all costs (test with follow-up purpose) incurred from the physician visit by the health care provider. Figure 3 summarises the main unit cost estimates for HPV-related genital disease outcomes.

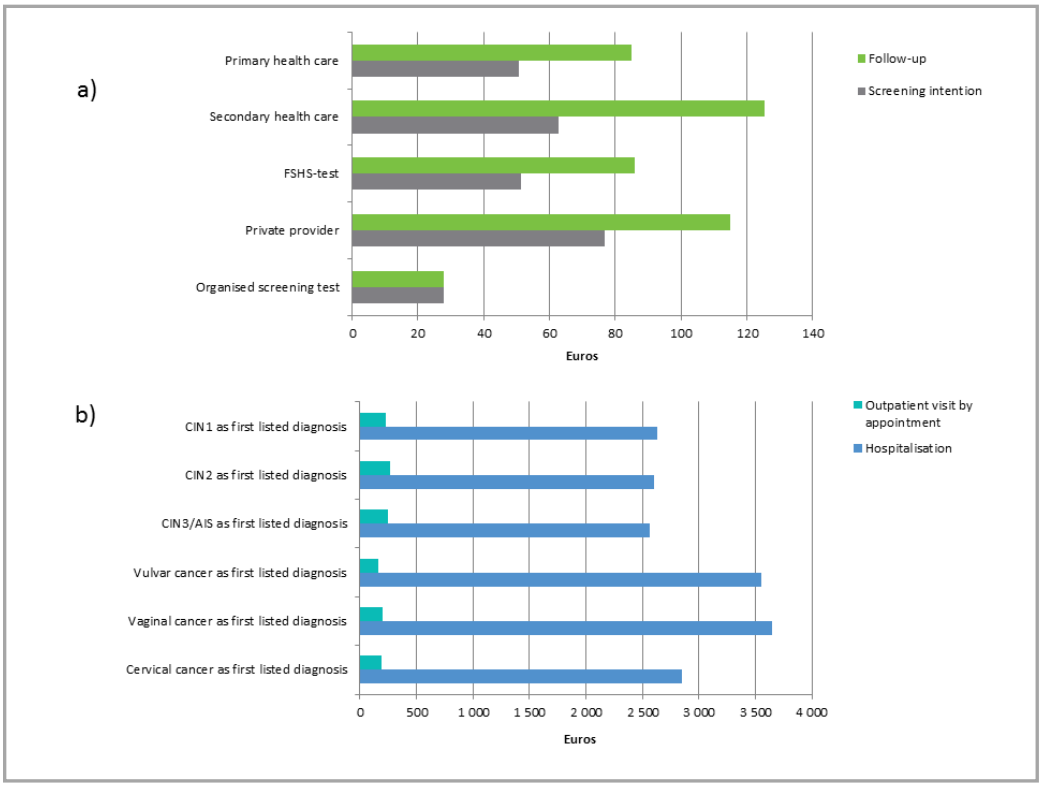

Figure 3. The main unit cost estimates in the HPV cost of illness study, euros at 2010 price level. (a) Pap-testing costs include the unit price for the test and half (tests with screening intention) or the whole (follow-up tests) prices of a visit to a physician. (b) Secondary health care costs. Average unit cost per hospitalisation or outpatient visit, estimates include diagnostic and treatment procedures (cost accounting data from the Hospital District of Helsinki and Uusimaa)

The average health care cost per case for a given outcome was derived by assigning the unit costs to the events. The cost per case included the costs of managing and treating the disease outcome for one or several years. If the health care costs were spread over several years, the cost per case was derived by summing up the estimated costs of the consecutive years. The years before diagnosis are referred to as pre-diagnostic years and the years after diagnosis as the post-diagnostic years.

In the first economic evaluation of the PCV7 programme (PCV7-I) and the economic evaluation of the influenza programme (II), the cost per case was delimited to one post-diagnostic year, with the exception of pneumococcal meningitis with hearing impairment. In the economic re-evaluation of the PCV7 programme (PCV7-II), the cost per case included the management and treatment costs of three post-diagnostic years (pneumococcal meningitis outcomes) or one post-diagnostic year (all other outcomes). The health care cost of the hearing impairment due to pneumococcal meningitis (PCV7-I, PCV7-II) was estimated for the lifetime. Cases in secondary health care were treated either as inpatient or outpatient. In the first economic evaluation of the PCV7 programme (PCV7-I), all cases of meningitis and bacteremia and 51% of pneumonia cases (191) were assumed to be treated as inpatients. In the economic re-evaluation (PCV7-II), all cases of meningitis, 92% cases of bacteremia, and 60% of pneumonia cases were estimated to be treated as inpatients among children aged 0 to 4 years (Health Care Register 2000–2006). Table 8 summarises the average total medical cost per case for pneumococcal- and influenza-related disease outcomes.

Table 8. Average undiscounted total medical cost per case[1] of pneumococcal- and influenza-related disease outcomes at 2010 price level

	Pneumococcal-related disease outcomes				
	PCV7-I (I)	PCV7-II			
	0–4y	0–4y	5–19y	20–64y	65+y
Meningitis, no complications	9113	12 621	9005	22 628	18 516
Meningitis with neurologic sequelae	9113	17 881	11 799	26 480	22 466
Meningitis with hearing impairment	49 883	105 618	74 024	50 322	26 230
Bacteremia	2849	1840	1805	8976	6487
Pneumonia, secondary health care	1389	1285	1850	4817	4740
Pneumonia, primary health care	N/A	181	199	202	187
AOM	119	108	N/A	N/A	N/A
Tympanostomy	1027	935	N/A	N/A	N/A
Adenotomy	1474	N/A	N/A	N/A	N/A
Tympanostomy and adenotomy[2]	1522	N/A	N/A	N/A	N/A
	Influenza-related disease outcomes (II)				
		0–4y	5–13y		
Influenza with					
no complications		70	70		
acute otitis media		223	242		
outpatient pneumonia		245	245		
sinusitis		82	82		
severe, outpatient care		323	323		
severe, inpatient care		2368	1977		

[1]Estimates in this table are presented in broader age groups. In the analysis, estimates varied by 1-year age bands.
[2]Simultaneously done

In the cost of illness study of HPV, the average cost per cancer and dysplasia case included 3 pre-diagnostic years and 9 post-diagnostic years. In other HPV-related outcomes the corresponding costs included 4 (minor cytological abnormalities) or 5 (external genital warts) post-diagnostic years (Figure 4).

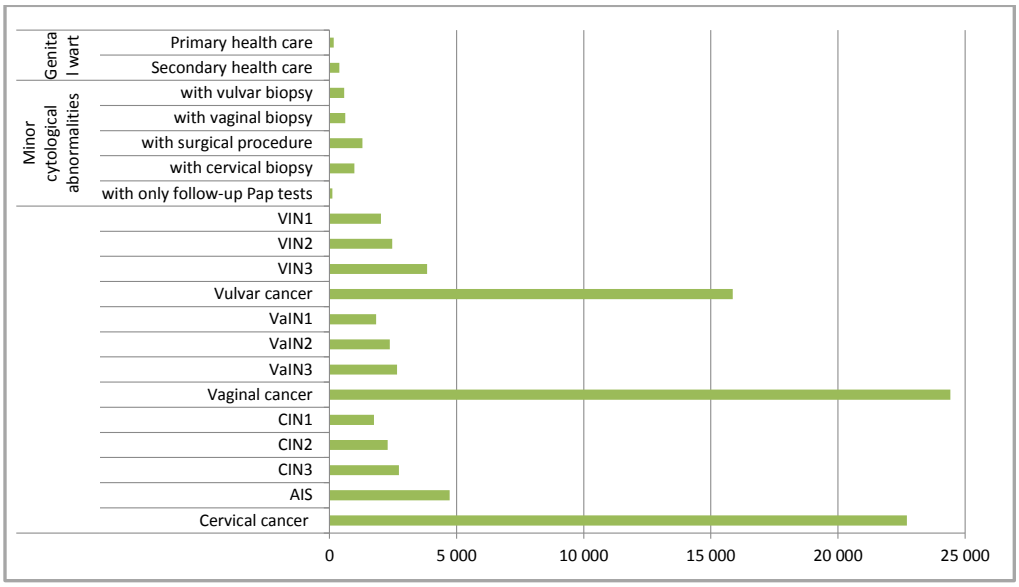

Figure 4. Average undiscounted cost per case of HPV-related disease outcomes at the 2010 price level

4.2.2.3 Other costs

In the first economic evaluation of the PCV7 programme (PCV7-I) and the influenza programme (II) we estimated the productivity costs due to parental work absenteeism and the travel costs of visits to primary or secondary care due to illness. Parental work absenteeism was estimated only for children <10 year olds, since Finland has a system of paid temporary care leave for one of the parents for a maximum of 4 days when a child <10 years of age suddenly gets ill. Parental work absenteeism was assumed to occur for under school-aged children attending out-of-home day care (200) and for school-aged children whose mothers participated in the labour market (OSF). In the economic evaluation of the influenza vaccination programme, we also estimated the parental work absenteeism and travel costs for taking the child to the site of vaccination.

Two prospective epidemiological studies were used to obtain the duration of parental absence due to influenza-related outcomes (108) and due to AOM (201). In the first economic evaluation of PCV7 (PCV7-I), we assumed the parental work absenteeism to be the same in outpatient pneumonia as in AOM (1.3 days per episode). For inpatient cases (meningitis 9.9

days, bacteremia 3.5 days, and pneumonia 3.3 days) we used the average number of inpatient days as an approximation of the duration of parental work absenteeism. In the first economic evaluation of PCV7 (PCV7-I), in addition, we evaluated the lost earnings due to premature death (IPD) and morbidity (hearing impairment due to pneumococcal meningitis).

The average gross income of Finnish employees was used to value production losses. Average travel cost per visit in primary health care or to an emergency department was obtained from a Finnish study (202).

4.2.3 Health-related Quality-Adjusted Life-Years (QALYs) lost for potentially vaccine-preventable disease outcomes

Estimates of the impact of the disease outcomes on the health-related quality of life were mainly obtained from the literature (Table 9). Finnish estimates were available only for a few conditions. The QALY loss following the hearing impairment (unpublished estimate) due to pneumococcal meningitis and post-treatment cancer survivors (203) were obtained from the Finnish Health 2000 Survey (204), which is a national health survey carried out in Finland in 2000–2001. The QALY loss following an abnormal cervical cytology was obtained from the prospective arm of an observational study of women referred for colposcopy at the Helsinki University Hospital in 2007–2010 (205).

The QALY loss estimates for childhood disease outcomes are particularly scarce. The natural development in growth and cognitive and functional abilities of the child, among other things, make measuring the health-related quality of life for the child more complex than that of adults (206). Thus, with the exception of AOM (207), we used QALY loss estimates of adults for all other pneumococcal disease outcomes in children. Although a health-related quality of life was not assessed in the original publication (II), in this study the QALY loss for influenza illness was obtained from a study assessing the impact of pandemic influenza on health-related quality of life in 7 regions of England (208). In the influenza-like illness control group, 30% were children younger than 16 years. The expected life years lost due to death from IPD and cervical, vaginal, and vulvar cancers were estimated from the age- and gender-specific life expectancy of the Finnish population (OSF) under the assumption that the case fatalities would have had an average life expectancy and all life years were lived in perfect health.

Table 9. QALY loss per case due to disease outcomes

	QALY loss per case	Reference
Pneumococcal-related disease outcomes (PCV7-I, PCV7-II)		
Bacteraemia	0.006	Assumption
Meningitis	0.006	Assumption
Profoundly deaf (first y)[1]	0.216	(204)
Profoundly deaf (subsequent y)[1]	0.054	(204)
Needs hearing-aid[1]	0.054	(204)
Moderate hearing loss[1]	0.054	(204)
Pneumonia, outpatient	0.004	(209)
Pneumonia, inpatient	0.006	(209)
AOM	0.005	(207)
Tympanostomy and/or adenotomy	0.005	Assumption
Influenza-related disease outcomes (II)	0.0075	(208)
HPV-related disease outcomes (III, IV)		
Cervical intraepithelial neoplasia (CIN1, CIN2, CIN3)[1]	0.0177	(205)
Vaginal intraepithelial neoplasia (VaIN1, VaIN2, VaIN3)[1]	0.0177	(205)
Vulvar intraepithelial neoplasia (VIN1, VIN2, VIN3)[1]	0.0177	(205)
Minor cytological abnormalities		
with only follow-up Pap tests[1]	0.004	(205)
with cervical biopsy[1]	0.004	(205)
with surgical procedure[1]	0.0177	(205)
Cervical, vaginal, and vulvar cancer[2]		
Stage I		
Year of treatment	0.32	(210)
2nd - 5th post-treatment year	0.03	(182)
6th + post-treatment years	0.018	(203)
Stage II		
Year of treatment	0.44	(210)
2nd - 5th post-treatment year	0.1	(182)
6th + post-treatment years	0.1	(182)
Stage III – IV		
Year of treatment	0.52	(210)
2nd - 5th post-treatment year	0.38	(182)
6th + post-treatment years	0.38	(182)
Genital warts	0.039	(211)

[1] QALY loss measured by the 15D other values measured by EQ-5D
[2] Mean loss of QALYs for cervical cancer was adjusted for the age group distribution of each cancer and the respective survival rates

4.3 Effectiveness of the PCV7 programme

In both economic evaluations of the PCV7 programme (PCV7-I, PCV7-II), the effectiveness of the programme on the vaccinated individuals was estimated using the vaccine efficacy estimates from the Northern California Kaiser Permanente (NCKP) vaccine trial (IPD, pneumonia, otologic surgical procedures) and the Finnish Otitis Media (FinOM) vaccine trial (AOM) (44, 54, 55). Table 10 summarises the vaccine efficacy estimates and the references. We assumed that the serotype distribution in IPD were comparable in Finland and Northern California according to the reported serotype distributions and made no serotype adjustments to the vaccine effectiveness estimates (193, 212, 213).

In the first economic evaluation of the PCV7 programme (PCV7-I), we used the per-protocol efficacy estimate for AOM (44) and the intention-to-treat estimates for all other outcomes (54, 55). The per-protocol estimate for AOM (6%) in the FinOM trial (44) was used since it was almost the same as the intention-to-treat estimate in the NCKP trial (6.4%) (54). In the economic re-evaluation of the PCV7 programme (PCV7-II), we used the per-protocol efficacy estimate for all-cause pneumonia and the intention-to-treat estimates for all other outcomes (54, 55, 214). For all-cause pneumonia (pneumonia treated in primary health care), the per-protocol estimate was lower than the intention-to-treat estimate (55). The former was selected because we wanted to be especially conservative.

AOM is known to be a common complication of upper respiratory tract infection (Heikkinen 2003). The vaccine does not prevent the preceding upper respiratory infection but it prevents some of the physician visits due to it. In other words, the child might seek medical care for the upper respiratory infection even though the episode of AOM is prevented. Thus, we assumed that the vaccine programme reduces all AOM-related sick visits to physicians as well as antibiotic prescribing by 4% among vaccinated individuals (214). In both studies, we assumed that the direct vaccine protection lasted for 5 years.

In the first economic evaluation of the PCV7 vaccination programme (PCV7-I), no indirect herd effects of the vaccination programme on the unvaccinated population were taken into account and in the base case analysis, a four-dose programme was assumed according to the manufacturer's recommendation at the time. *In the economic re-evaluation of the PCV7 vaccination programme (PCV7-II)*, we considered three scenarios. In the vaccinated effects scenario, only the effects of the vaccination programme on the vaccinated individuals were included in the analysis. In the indirect effects scenarios, the indirect herd effects on IPD (scenario A) and on both IPD and pneumonia (scenario B) on the unvaccinated population were also included in the analysis. Vaccine effectiveness after the first dose for the vaccinated was derived from a study that investigated the effectiveness of incomplete schedules of the vaccination programme against IPD (215). In this study the effectiveness of the vaccination programme against IPD after the first, second and third dose was 73%, 96% and 95%, respectively. Thus, we assumed the reduction after the first dose to be 76.8% (73/95) of the used estimate for each pneumococcal disease outcome. After the second dose, we assumed no reduction in the used estimate.

In the economic re-evaluation, the impact of the indirect herd effects of the PCV7 vaccination programme on the cost-effectiveness was investigated with static scenario analysis. In addition to the total effect on the vaccinated individuals, we assumed the vaccination programme to reduce 20% of the IPD cases among the unvaccinated population aged ≥5 years (indirect effects scenario A) or 20% of the IPD and 4% of the pneumonia cases treated in secondary health care in the same population (indirect effects scenario B). At the time the analysis was conducted the post-vaccination estimates from the USA were the only source for the indirect effect estimate. The assumed reduction in IPD among the unvaccinated was roughly based on the first post-vaccination year estimates in the USA where the rate of IPD decreased 32% in those aged 20–39 years, 8% in those aged 40–64 years, and 18% in those aged ≥65 years (68). The indirect herd effect on pneumonia on the unvaccinated population was assumed to be almost half of the total effect on the vaccinated. The reduction in the unvaccinated population was assumed to consist of both the reduction in vaccine-type disease induced by herd protection and the increase in non-vaccine-type disease due to replacement.

Table 10. The vaccine efficacy estimates against pneumococcal disease outcomes used in evaluating the effect of vaccination programme on the vaccinated individuals

	PCV7-I	PCV7-II	Reference
All IPD	89.1	89.1	(54)
Pneumonia			
Clinical pneumonia with a positive radiograph	17.7	N/A	(55)
Clinical pneumonia and radiograph obtained[1]	N/A	8.9	(55)
All clinical pneumonia[2, 3]	N/A	4.3	(55)
All AOM[3]	6.0	N/A	(44)
AOM related visits to physician	N/A	4.0	(214)
Otologic surgical procedures	20.3	20.3	(54)

N/A, not applicable

[1]Pneumonia treated in secondary health care

[2]Pneumonia treated in primary health care

[3] Per-protocol estimates, intention-to-treat estimates for all other outcomes

4.4 Effectiveness of influenza vaccination programme in children

In the base case, we assumed the inactivated influenza vaccination programme to reduce 80% of the influenza cases in vaccinated individuals (120, 216). We assumed no indirect herd effect of the influenza vaccination programme on unvaccinated individuals.

4.5 Sensitivity analysis in the economic evaluations of PCV7 and influenza vaccination programmes

In the economic evaluations of the PCV7 programme (PCV7-I, PCV7-II), we investigated the effects of variation in the key parameters of the model in the scenario analyses. In the economic re-evaluation of the PCV7 vaccination programme (PCV7-II), a multivariate probabilistic sensitivity analysis was conducted from the health care payer perspective for the indirect effects scenarios A and B. The vaccine price, discount rate, and vaccine effectiveness estimates were held constant and the other parameters of the model were allowed to change within their specified ranges (Table 11). Since less severe IPD cases were assumed to be under-detected in Finland, the base case value was assumed in the sensitivity analysis to be the minimum value. The parameter of the IPD incidence ranged from the base case value to double the base case. The costs and QALY-losses of pneumococcal disease outcomes for the unvaccinated and vaccinated cohort were simulated 15 000 times. An ICER was calculated for each re-calculated mean values for costs and QALY-losses. The results are plotted on a cost-effectiveness plane and associated cost-effectiveness acceptability curve. The given distributions of input parameters were mainly based on data and if no data were available we defined a uniform distribution.

Table 11. Distributions used in the probabilistic sensitivity analysis. SD refers to the standard deviation of the respective log-normal distribution. Mean values of the parameters are listed in Tables 3, 8 and 9.

	Distribution	Range	SD 0–4y	SD 5–19y	SD 20–64y	SD 65+y
Incidence rate						
Meningitis	Uniform	0 to +100%				
Bacteraemia	Uniform	0 to +100%				
Pneumonia, secondary health care	Log-normal		0.0244	0.0263	0.0119	0.0097
Pneumonia, primary health care	Log-normal		0.0283	0.0198	0.0136	0.0162
AOM	Log-normal		0.0020			
Tympanostomy	Uniform	± 20 %				
Sequelae after pneumococcal disease outcomes						
Mortality in IPD	Log-normal		2.9252	1.7177	0.1537	0.1485
Mortality in pneumonia	Log-normal		2.2361	1.8257	0.1547	0.1322
Meningitis, neurologic sequelae	Uniform	± 20 %				
Meningitis, hearing impairment	Uniform	± 20 %				
Cost (EUR) per case						
Meningitis, no complication	Log-normal		12 204	9205	27 572	30 069
Meningitis, neurologic sequelae	Log-normal		7552	2277	8390	7767
Meningitis, hearing impairment	Uniform	± 20 %				
Bacteraemia	Log-normal		2041	2053	14 875	14 026
Pneumonia, secondary health care	Log normal		2473	2491	17 133	18 629
Pneumonia, primary health care	Uniform	± 20 %				
AOM	Uniform	± 20 %				
Tympanostomy	Uniform	± 20 %				
QALY loss / case by disease outcome	Uniform	± 20 %*				

Estimates in this table are presented in broader age groups. In the analysis, estimates varied by 1-year age bands.
* Parameter was varied separately for each outcome.

In the economic evaluation of the influenza vaccination programme in children, we conducted several univariate sensitivity analyses, for example, on assumed vaccine efficacy and cost per dose. We used probabilistic sensitivity analysis to assess the effects of uncertainties in disease probabilities and in disease costs. Dirichlet distributions with Dirichlet parameter values set equal to the observed disease counts (as obtained from data (108)) were applied to form uncertainty distributions for the age-specific probabilities of different influenza-related disease outcomes. For each outcome-related cost, a lognormal density was formed s.t. 90% of the probability mass was assigned within the ± 60% range with respect to the base value. For costs that varied with age, simulated values were adjusted according to the proportions in the age-specific base values. The vaccine price was held fixed and the costs were simulated 10 000 times.

5 Results

5.1 Current burden and costs of diseases potentially preventable by vaccinations

The estimated annual burden and costs of pneumococcal-, influenza- and HPV-related disease outcomes before the implementation of the vaccination programmes are shown in Table 12. The pneumococcal-related disease burden was estimated in children aged 0–4 years in the first economic evaluation of the PCV7 programme (PCV7-I) and in all age groups in the economic re-evaluation of the PCV7 vaccination programme (PCV7-II). The influenza-related burden of disease was estimated in children aged 0.5–13 years (II) and HPV-related in women aged ≥15 years (III, IV).

5.1.1 Number of cases

In children aged 0–4 years, there were estimated to be annually 69 IPD cases in the first economic evaluation of the PCV7 programme (PCV7-I) and 101 IPD cases in the economic re-evaluation (PCV7-II). The corresponding numbers for potentially pneumococcal pneumonia were 8165 and 2966, respectively. The difference in IPD cases was due to different calendar years the data were retrieved from and, in pneumonia cases, due to different data sources. In both economic evaluations of the PCV7 programme, 250 000 episodes of AOM due to all causative pathogens were estimated to occur in children aged 0–4 years. In the economic re-evaluation of the PCV7 programme (PCV7-II), of the annual 688 cases of IPD and 34 897 cases of potentially pneumococcal pneumonia in all age groups, children aged 0–4 years accounted for 101 (15%) and 2966 (8%) cases, respectively. The all-cause AOM cases were estimated only for children aged <5 years old.

Without the vaccination programme, in children aged 6 months to 13 years, there were estimated to be 121 885 cases of symptomatic influenza annually, corresponding to an annual attack rate of 15%. These children had as a complication of influenza 18 076 cases of acute otitis media, 4 572 cases of sinusitis and 2 474 cases of outpatient pneumonia.

Before the anticipated effects of the vaccination programme, there are annually on average 153 cervical, 16 vaginal and 72 vulvar cancer cases in Finland. An average of 1033 new cases of CIN3/AIS, 1865 new cases of CIN1-2 and 34 400 new cases of minor cytological abnormalities are detected annually. Annually almost 4000 women receive medical care due to external genital warts.

An annual average of 446 000 Pap tests are carried out for screening purposes, of which 177 000 (40%) are carried out in the organised programme, 24 000 (5%) in secondary health care and 244 000 (55%) as opportunistic tests. In addition, there are 84 000 Pap tests carried out as a follow-up of previously detected cervical abnormalities.

5.1.2 Life-years and QALYs lost

Approximately one child aged 0–4 years was estimated to die due to IPD every year (PCV7-I, PCV7-II). In all age groups, there were estimated to be an average of 219 deaths due to IPD and potentially pneumococcal pneumonia, corresponding to 3 421 estimated undiscounted life-years lost (PCV7-II). Of the estimated annual 94 deaths and 1737 life-years lost due to IPD, children aged 0–4 years accounted for one (1.5%) of the death cases and 111 (6%) of the life-years lost. We assumed no influenza- associated deaths to occur in children (II). An annual average of 56, 12 and 30 female deaths were due to cervical, vaginal, and vulvar cancer corresponded to 993, 127 and 346 estimated undiscounted life years lost, respectively (III).

In children aged 0–4 years, the estimated potentially pneumococcal attributable QALYs lost were 1446 and 1435 in the first (PCV7-I) and second (PCV7-II) economic evaluation of the PCV7 programme. In children aged 0–4 years, all-cause AOM accounted for 91% of all pneumococcal attributable QALYs lost (PCV7-I, PCV7-II). In all age groups, 3421 (70%) of the total 4900 undiscounted QALYs lost were life-years lost due to pneumococcal-related deaths (PCV7-II). Of the estimated annual 914 non-fatal QALYs lost due to influenza-related disease outcomes in children aged 0.5–13 years, <3 year olds and <5 year olds accounted for 190 (21%) and 338 (37%), respectively. Life-years lost accounted for 1466 (62%) of the 2368 annual undiscounted QALYs lost due to HPV-related disease outcomes in women.

5.1.3 Health care provider costs

In children aged 0–4 years, the estimated health care costs were EUR 57.4 million in the first economic evaluation of the PCV7 programme (PCV7-I) and EUR 39.3 million in the economic re-evaluation (PCV7-II). The lower estimated health care costs in the re-evaluation were due to a lower incidence of pneumonia and the exclusion of adenotomies from the analysis. Of these estimated health care costs, IPD accounted for 0.5% and 1%, pneumonia 21% and 6% and all-cause AOM 79% and 93% in the first and second evaluation, respectively. In the economic re-evaluation in all age groups, the estimated annual health care costs of IPD without the vaccination programme were EUR 5.0 million and of potentially pneumococcal pneumonia EUR 98.6 million. The costs of all-cause AOM were estimated to be EUR 36.6 million in children aged 0–4 years.

In children aged 6 months to 13 years, the estimated health care costs of influenza-associated outcomes were EUR 13.0 million, of which the costs of primary health care visits of uncomplicated cases accounted for EUR 6.7 million (52%) and the costs of AOM accounted for EUR 4.3 million (33%) (II). In children aged 6 months to 4 years the costs of AOM accounted for EUR 3.5 million (54%) of the total health care costs (EUR 6.5 million).

The estimated annual health care costs of HPV-related genital disease outcomes in women were EUR 22.3 million, of which the management and treatment of detected cases of CIN and minor cytological abnormalities accounted for EUR 15.5 million (69%) (III). The annual cost of Pap tests taken for screening purposes was EUR 22.4 million of which EUR 5.0 million (22%) were due to tests taken in organised screening, EUR 1.5 million (7%) in secondary health care and EUR 15.9 million (71%) in opportunistic screening (IV).

5.1.4 Other costs

We estimated the travel and productivity costs of the caregiver from illness in children in the first economic evaluation of the PCV7 programme (PCV7-I) and in the economic evaluation of the influenza programme (II). In addition, in the economic evaluation of the influenza vaccination programme we estimated the corresponding costs of taking the child to the site of vaccination.

In children aged 0–4 years, the estimated annual travel costs due to pneumococcal-related disease outcomes were EUR 2.3 million. The estimated annual productivity costs due to parental work absenteeism were EUR 19.9 million and due to hearing impairment EUR 0.02 million.

Travel costs due to influenza illness were EUR 0.4 million in children aged 0.5–4 years and EUR 0.6 million in children aged 5–13 years. In corresponding age groups, the travel costs due to influenza vaccination were EUR 1.5 million and EUR 3.0 million, respectively.

Productivity costs of parental work absenteeism due to influenza illness in children aged 0.5–4 years were EUR 10.9 million and in children aged 5–13 years EUR 23.0 million. In corresponding age groups, the productivity costs due to influenza vaccination were EUR 2.2 million and EUR 8.9 million, respectively.

Table 12. Annual burden and health care costs of pneumococcal, influenza and HPV -related diseases potentially preventable by vaccinations before implementation of the vaccination programme in Finland

	Number of cases			Undiscounted QALYs/life-years lost[4]			Undiscounted health care costs		
	0–4y	**5–14y**	**15+y**	**0–4y**	**5–14y**	**15+y**	**0–4 y**	**5–14y**	**15+y**
Pneumococcal-related disease outcomes (PCV7-I)				**1446**			**57 405 429**	**N/A**	**N/A**
Study population: 57 574 live births									
IPD	69	N/A	N/A	82	N/A	N/A	279 982	N/A	N/A
All-cause pneumonia	8165	N/A	N/A	41	N/A	N/A	11 845 965	N/A	N/A
All-cause AOM	249 683	N/A	N/A	1323	N/A	N/A	45 279 483	N/A	N/A
IPD death: cases / life-years lost	0.9	N/A	N/A	75	N/A	N/A	N/A	N/A	N/A
Pneumococcal-related disease outcomes (PCV7-II)				**1435**	**18**	**3447**	**39 311 683**	**2 088 169**	**98 793 844**
Study population: 58 000 live births									
IPD	101	15	572	113	7	1628	272 322	46 823	4 654 672
Potentially pneumococcal pneumonia	2966	2676	29 255	13	11	1819	2 412 838	2 041 347	94 139 171
All-cause AOM[1]	251 528	N/A	N/A	1308	N/A	N/A	36 626 523	N/A	N/A
IPD death: cases / life-years lost	1.4	0	92	111	6	1620	N/A	N/A	N/A
Pneumonia death: cases / life-years lost	0	0	125	0	0	1684	N/A	N/A	N/A
Life-years lost, total				111	6	3305			
Influenza-related disease outcomes (II)	**45 086**	**76 799**	**N/A**	**338**	**576**	**N/A**	**6 527 911**	**6 481 330**	**N/A**
Study population, 0.5-13 yrs[2]	252 000	504 000							
Influenza and AOM	14 894	3183	N/A	112	24	N/A	3 497 529	771 818	N/A
Influenza and pneumonia (outpatient)	1313	1162	N/A	10	9	N/A	321 339	285 248	N/A

Influenza and sinusitis	1119	3453	N/A	8	26	N/A	93 065	287 926	N/A
Influenza, severe	922	508	N/A	7	4	N/A	729 522	321 869	N/A
Influenza, uncomplicated	26 838	68 493	N/A	201	514	N/A	1 886 456	4 814 469	
HPV-related disease outcomes[3] (III)						**2480**			**22 337 787**
Study population, females 2008			2 278 674						
Cervical cancer	N/A	N/A	153	N/A	N/A	1294	N/A	N/A	3 580 983
AIS, CIN1-3	N/A	N/A	2898	N/A	N/A	254	N/A	N/A	6 808 384
Vaginal cancer	N/A	N/A	16	N/A	N/A	149	N/A	N/A	404 007
VaIN1-3	N/A	N/A	123	N/A	N/A	10	N/A	N/A	291 669
Vulvar cancer	N/A	N/A	72	N/A	N/A	427	N/A	N/A	1 234 915
VIN1-3	N/A	N/A	160	N/A	N/A	14	N/A	N/A	496 902
Cases of minor cervical cytological abnormalities	N/A	N/A	34 432	N/A	N/A	220	N/A	N/A	8 662 249
Genital wart cases	N/A	N/A	3850	N/A	N/A	112	N/A	N/A	858 678
Cervical, vaginal, and vulvar cancer death: cases / life-years lost	N/A	N/A	98	N/A	N/A	1466	N/A	N/A	N/A
Total, tests with screening intention (IV)	N/A	N/A	**445 674**	N/A	N/A	N/A	N/A	N/A	**22 402 840**
Organised screening tests	N/A	N/A	177 320	N/A	N/A	N/A	N/A	N/A	4 966 732
Opportunistic tests with screening intention	N/A	N/A	268 354	N/A	N/A	N/A	N/A	N/A	17 436 108

N/A, not applicable
[1]In the analysis AOM cases were estimated only for the children aged 0–4 years
[2]Age groups were exceptional for the influenza related outcomes: 0.5–4 years and 5–13 years
[3]HPV outcomes: annual averages in 1999-2008 (cervical, vaginal, and vulvar cancer) or in 2004–08 (all other outcomes)
[4]Figures indicate QALYs lost unless specified as life-years lost in the respective row.

5.2 Economic evaluation of pneumococcal conjugate vaccination programme

The results of the economic evaluations of the PCV7 programme (PCV7-I, PCV7-II) from the health care payer perspective with base-case parameters are shown in Table 13. All costs are presented at the 2010 price level using a 5% discount rate for future benefits and costs according to the recommendations at the time these studies were conducted.

5.2.1 Reduction in the burden of disease due to the vaccination programme

In children aged 0–4 years, when taking into account only the direct effect of the vaccination programme on the vaccinated 0–4-year-olds, the vaccination programme was estimated to result in 108.5 QALYs gained annually in the first economic evaluation of the PCV7 programme (PCV7-I) and 79.3 QALYs gained in the corresponding 'vaccinated effects scenario' of the economic re-evaluation (PCV7-II). In the economic re-evaluation, we estimated the PCV7 programme to prevent fewer pneumonia and AOM cases compared to the first evaluation since we applied lower vaccine effectiveness estimates for both pneumonia and AOM and estimating lower incidence rate for pneumonia. In children aged 0–4 years, the PCV7 programme was estimated to prevent an annual average of 0.9 and 1.2 IPD deaths in the first (PCV7-I) and second (PCV7-II) economic evaluation corresponding to 17.2 and 23.7 discounted life-years gained, respectively.

In the economic re-evaluation of the PCV7 vaccination programme (PCV7-II), we estimated that the PCV7 programme would indirectly prevent annually 117 IPD cases and 19 IPD deaths in the 'Indirect effects scenario A and B' and additionally 818 pneumonia cases and 5 pneumonia deaths in the 'Indirect effects scenario B'. When taking into account both the direct and indirect herd effects of the PCV7 vaccination programme the vaccination programme was estimated to result annually in 276 QALYs gained and 220 life-years gained in the 'indirect effects scenario A' and 324 QALYs gained and 263 life-years gained in the 'indirect effects scenario B'.

5.2.2 Cost savings and cost-effectiveness from the health care provider perspective

In children aged 0–4 years, the vaccination programme was estimated to save annually EUR 7.2 million in medical costs in the first economic evaluation of the PCV7 programme and EUR 3.0 million in the economic re-evaluation (Table 13). In the re-evaluation (PCV7-II), taking into account the direct and indirect herd effects of the vaccination programme, we estimated a saving annually of in total EUR 4.0 million in the 'Indirect effects scenario A' and EUR 7.7 million in the 'Indirect effects scenario B'. The cost of vaccinating a birth cohort was estimated to be EUR 13.1 and EUR 9.7 million in the first (PCV7-I) and second (PCV7-II) economic evaluations, respectively.

When taking into account only the direct effect of the vaccination programme the estimated discounted cost per QALY gained was EUR 54 576 in the first evaluation and EUR 83 759 in the economic re-evaluation. Correspondingly, the cost per life-year gained was EUR 345 027 and EUR 279 496. When taking into account the estimated direct and indirect herd effects on IPD (scenario A) of the vaccination programme, the cost per QALY gained was EUR 20 558 and the cost per life-year gained was EUR 25 839 (PCV7-II). When taking into account the estimated direct and indirect herd effects on IPD and pneumonia (scenario B), the cost per QALY gained reduced to EUR 5983 and cost per life-year gained to EUR 7360. All estimates for cost-effectiveness ratios are presented from the health care provider perspective.

5.2.3 Cost savings and cost-effectiveness from the societal perspective

In the first evaluation of the PCV7 vaccination programme (PCV7-I), we estimated the reduction in the pneumococcal-related travel costs to be EUR 0.17 million and in productivity costs EUR 1.52 million (EUR 1.5 million and EUR 0.02 million due to, respectively, parental work absenteeism and hearing impairment) in children aged 0–4 years. From the societal perspective, the estimated discounted cost per QALY gained was EUR 39 121 and cost per life-year gained was EUR 247 323. Unlike in the original publication (I), the results from the societal perspective presented here do not include the productivity costs due to averted mortality in order to avoid double counting the mortality costs, as the gain in the life-years already manifests the mortality costs in the denominator of the ratio.

Table 13. Results of the economic evaluations of the PCV7 programme. Estimated annual outcomes prevented and health care costs saved by the vaccination programme versus no vaccination and incremental cost-effectiveness ratios (ICERs). Costs and benefits discounted at a 5% discount rate. Health care payer perspective. All costs presented at the 2010 price level.

	PCV7-I (I)[1]	PCV7-II		
		Vaccinated effects scenario[1]	Indirect effects scenario A[2]	Indirect effects scenario B[3]
Birth cohort / Vaccination coverage	57 574 / 100%	58 000 / 97%		
Outcomes prevented				
Pnc meningitis	4	3	7	7
Pnc bacteraemia	58	81	194	194
Pneumonia	1445	194	194	1012
All-cause AOM	14 982	9631	9631	9631
IPD deaths	0.9	1.2	20	20
Pneumonia deaths	N/A	N/A	N/A	5
Life-years gained	**17.2**	**23.7**	**219.8**	**263.2**
QALYs gained, total	**108.5**	**79.0**	**276.3**	**323.7**
IPD	19.0	24.5	221.8	221.8
Pneumonia	6.6	0.8	0.8	48.3
All-cause AOM	82.9	53.6	53.6	53.6
Treatment costs saved	7 197 610	3 048 425	3 984 297	7 726 551
IPD	242 766	197 673	1 133 542	1 133 542
Pneumonia	1 982 224	175 539	175 539	3 917 794
All-cause AOM	4 972 619	2 675 215	2 675 215	2 675 215
Total direct vaccination costs	**-13 119 688**	**-9 663 536**	**-9 663 536**	**-9 663 536**
Administration costs	-458 138	-559 335	-559 335	-559 335
Vaccine purchase[4]	-12 661 549	-9 104 202	-9 104 202	-9 104 202
Total health care costs	-5 922 078	-6 615 108	-5 679 239	-1 936 985
Cost / QALY gained	54 576	83 759	20 558	5983
Cost / Life-years gained	345 027	279 496	25 839	7360

N/A, not applicable
[1]Only direct effect of the vaccination programme on vaccinated individuals was assumed.
[2]Direct effect on the vaccinated and 20% reduction in IPD among unvaccinated population aged 5 years and older was assumed.
[3]Direct effect on the vaccinated and 20% reduction in IPD and 4% in pneumonia cases treated in secondary health care among unvaccinated population aged 5 years and older was assumed.
[4]Assumed vaccine price per dose EUR 60.7 in PCV7-I and EUR 52.3 in PCV7-II

5.2.4 Sensitivity analysis

The results of the economic evaluations of the PCV7 vaccination programme with different discount rates and half of the price in the base-case are shown in the Table 14. The discount rate influences the results of the cost-effectiveness analysis mostly by the impact on benefits (life-years gained). When only taking into account the direct effect of the vaccination programme and a vaccine price of EUR 25 per dose, the vaccination programme was cost saving in the first economic evaluation (PCV7-I) and the cost per QALY decreased to EUR 25 462 in the economic re-evaluation (PCV7-II) from the health care provider perspective.

In the sensitivity analysis, we also investigated the impact of a lower indirect herd effect in IPD on the base case results (Indirect effects scenario A). When we assumed only a 10% or 5% reduction in IPD in unvaccinated population aged 5 years and older, the cost per QALY increased from EUR 20 490 to EUR 34 566 or EUR 49 631, respectively.

Table 14. Results of the economic evaluation of the PCV7 vaccination programme in different discount rates from the health care provider perspective. All costs are presented at the 2010 price level.

	PCV7-I(I)[1]	PCV7-II		
		Vaccinated effects scenario[1]	Indirect effects scenario A[2]	Indirect effects scenario B[2]
Cost / QALY gained				
Discount rate 5%, base case	54 576	83 759	20 558	5983
Discount rate 3%	45 875	70 098	17 044	4810
Discount rate 0%	29 256	41 807	11 295	3027
Vaccine price EUR 25 / dose	Cost saving	25 462	3891	Cost saving
Cost / Life-year gained				
Discount rate 5%, base case	345 027	279 496	25 839	7360
Discount rate 3%	211 087	182 579	20 750	5752
Discount rate 0%	72 750	103 900	86 322	24 947
Vaccine price EUR 25 / dose	Cost saving	84 963	4891	Cost saving

[1]Only direct effect in vaccinated individuals of the vaccination programme was assumed.
[2]Direct effect to the vaccinated and 20% reduction in IPD in unvaccinated population aged 5 years and older was assumed
[3]Direct effect to the vaccinated and 20% reduction in IPD and 4% in pneumonia cases treated in secondary health care in unvaccinated population aged 5 years and older was assumed.

In the second economic evaluation of PCV7 vaccination programme (PCV7-II), we conducted a multivariate sensitivity analysis from the health care payer perspective for the indirect effects scenarios A and B versus no vaccination. The costs and QALY-losses of pneumococcal disease outcomes for the unvaccinated and vaccinated cohort were simulated 15 000 times. In the cost-effectiveness plane (Figure 5), points below the red full line represent simulations in which the PCV7 vaccination programme was a cost-effective alternative at an assumed threshold of EUR 20 000 per QALY gained. The cost-effectiveness acceptability curves in Figure 6 were derived from the joint distribution of incremental costs and effects shown in Figure 5. The curve shows that the indirect effects scenario A (assuming direct effect to the vaccinated and 20% reduction in IPD in unvaccinated population aged ≥5 years) was cost-effective versus no vaccination in nearly 100% of simulations at the willingness to pay threshold of EUR 20 000 per QALY gained.

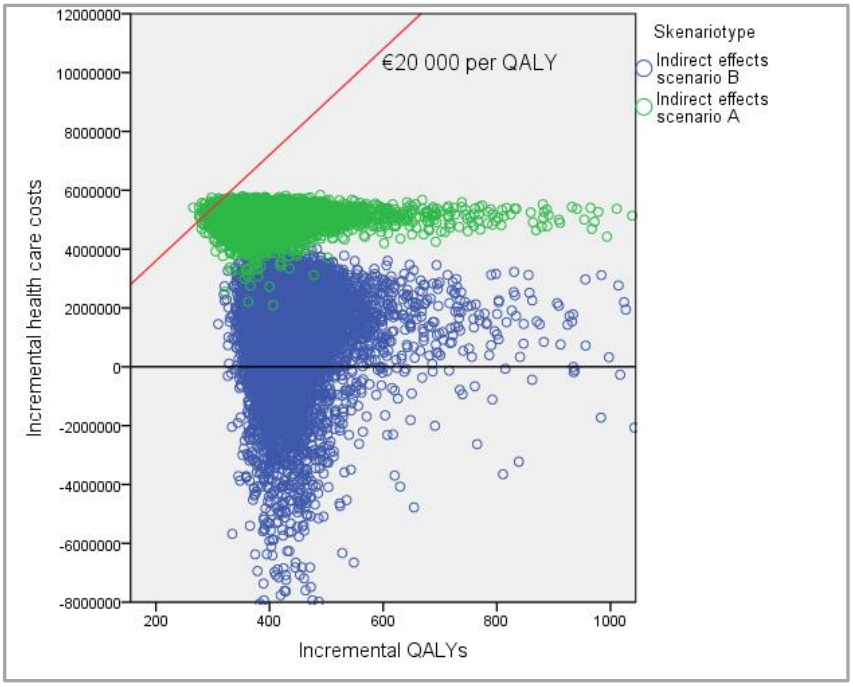

Figure 5. The Cost-effectiveness plane for incremental costs and effects of 'Indirect effects scenario A' and 'Indirect effects scenario B' versus no vaccination. EUR 20 000 per QALY gained threshold line indicated with the red line. Health care costs are presented at the 2010 price level and costs and benefits discounted at a 5% discount rate. Indirect effects scenario A: assuming a direct effect to the vaccinated and a 20% reduction in IPD in unvaccinated population aged ≥5 years. Indirect effects scenario B: assuming direct effect on the vaccinated and a 20% reduction in IPD and 4% in pneumonia cases treated in secondary health care in the unvaccinated population aged ≥5 years.

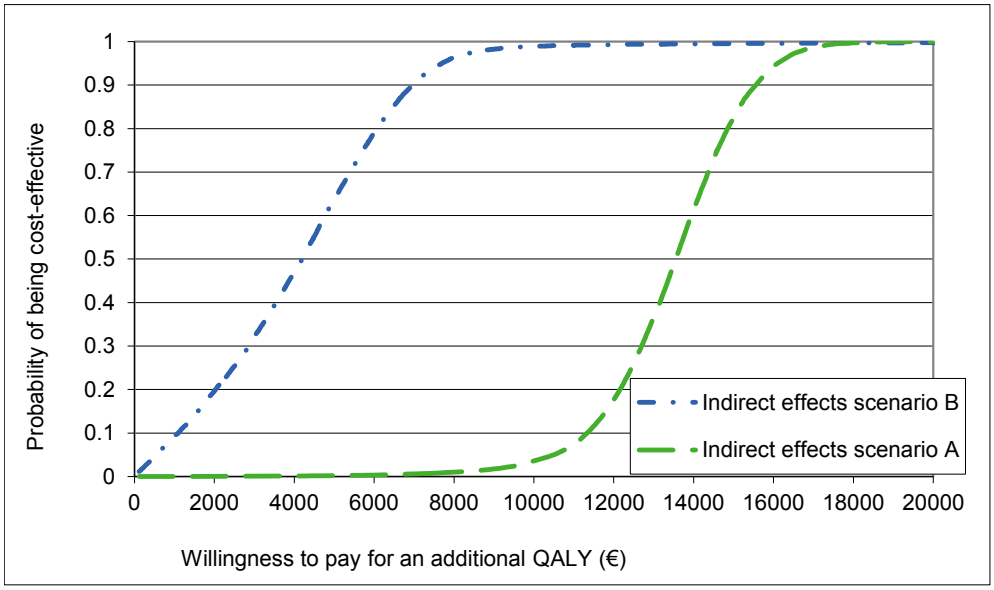

Figure 6. The cost-effectiveness acceptability curves derived from the joint density of incremental costs and incremental effects (QALYs gained) for the PCV7 vaccination programme. 'Indirect effects scenario A' and 'Indirect effects scenario B' were compared to no vaccination scenario from the health care payer perspective. Health care costs are presented at the 2010 price level and costs and benefits discounted at 5% discount rate. *Indirect effects scenario A*: assuming direct effect to the vaccinated and 20% reduction in IPD in unvaccinated population aged ≥5 years. *Indirect effects scenario B*: assuming a direct effect to the vaccinated and a 20% reduction in IPD and 4% in pneumonia cases treated in secondary health care in unvaccinated population aged ≥5 years.

5.3 Economic evaluation of influenza vaccination programme among healthy children

When the vaccine effectiveness was assumed to be 80% and the vaccination coverage 100%, a vaccination programme targeted to children aged 0.5–4 years prevented 36 069 cases of influenza corresponding to 271 QALYs gained and EUR 5.2 million medical costs saved (Table 15). In this age group influenza cases with AOM accounted for 33% (11 915) of the cases prevented and 54% (EUR 2.8 million) of the treatment costs saved. In children aged 5–13 years, influenza cases without complication accounted for 89% of the cases prevented and 74% of the treatment costs saved. From the health care provider perspective, the vaccination programme was cost saving in children aged 0.5–13 years.

Under base case assumptions, we estimated the increase in the influenza and influenza vaccination-related travel costs to be EUR 1.3 million and the reduction in productivity costs to EUR 5.9 million in children aged 0.5–4 years. The corresponding costs were EUR 2.9 million and EUR 7.3 million in children aged 5–13 years, respectively. The travel costs of taking the child to the site of vaccination exceeded the travel costs related to influenza illness. The societal perspective, furthermore, increased the savings gained from the vaccination programme.

In each age group, the savings exceeded the cost of the vaccination programme (remained cost-saving) with a vaccine efficacy of 60% and a reduction by 50% in the rate of visits to the emergency department. However, with a reduction by 50% in the rate of visits to primary care, the cost of the vaccination programme exceeded the savings among children over 6 years of age. We found that the cost of vaccine was highly influential on the results. At an assumed cost of EUR 11 per dose of the vaccine, the cost of the vaccination programme exceeded the savings in the aggregated age group of children aged 0.5–4 years. In the probabilistic sensitivity analysis using Monte Carlo simulations, we obtained the following 2.5%, 50% and 97.5% quantiles for the savings per vaccinated child (in euros): (4.1, 14.4, 30.3) in children aged <3 years, (4.0, 12.5, 25.4) in children aged <5 years and (3.5, 10.8, 21.9) in children aged <7 years.

Table 15. Results of the economic evaluation of the influenza vaccination programme in children with vaccine effectiveness of 80% and 60%. The effect of different vaccine effectiveness estimates on estimated annual outcomes prevented and health care costs saved by the vaccination programme versus no vaccination. All costs (EUR) are presented at the 2010 price level.

	Vaccine effectiveness 80%		**Vaccine effectiveness 60%**	
	0.5–4y	**5–13y**	**0.5–4y**	**5–13y**
Influenza cases prevented, total	**36 069**	**61 439**	**27 053**	**46 080**
Influenza and AOM	11 915	2546	8937	1910
Influenza and pneumonia (outpatient)	1051	929	788	697
Influenza and sinusitis	895	2762	672	2072
Influenza, severe	737	407	553	305
Influenza, uncomplicated	21 471	54 795	16 104	41 097
QALYs gained	**271**	**461**	**203**	**346**
Treatment costs saved	**5 222 447**	**5 185 190**	**3 916 992**	**3 888 832**
Influenza and AOM	2 798 083	617 487	2 098 663	463 102
Influenza and pneumonia (outpatient)	257 080	228 154	192 786	171 157
Influenza and sinusitis	74 459	230 345	55 838	172 764
Influenza, severe	583 626	257 593	437 768	193 073
Influenza, uncomplicated	1 509 200	3 851 611	1 131 937	2 888 737
Total direct vaccination costs	**-2 040 531**	**-3 340 136**	**-2 040 531**	**-3 340 136**
Administration costs	-1 189 345	-1 947 286	-1 189 345	-1 947 286
Vaccine purchase*	-851 186	-1 392 850	-851 186	-1 392 850
Health care costs saved	**3 181 916**	**1 845 054**	**1 876 461**	**548 696**
Cost / QALY gained	Cost saving	Cost saving	Cost saving	Cost saving
Saving (EUR) / vaccinated	12.6	3.7	7.4	1.1

*Assumed vaccine price per dose EUR 2.8.

5.4 Coverage and frequency of organised and opportunistic Pap testing

In Finland, women aged 30–60 years are invited for a test in an organised screening programme every 5 years. In addition, some municipalities also invite women aged 25 and/or 65 years. Of the 446 000 Pap tests taken annually for screening purposes, 60% were taken outside the organised programme. The 5-year coverage and frequency of Pap testing was estimated based on the Helsinki metropolitan region.

With the proportion increasing with age, 55% to 75% of women aged 30–64 years had an organised Pap test taken during the last 5 years. Furthermore, 51% of those attending the organised screening also had at least one Pap test taken outside the organised programme. About 60% of women in age groups 25–29 and 65–69 are invited to organised screening in the Helsinki metropolitan region. Therefore, the coverage of organised screening among women in these age groups was lower, at 33% and 46%, respectively.

The overall coverage of Pap testing was high, with as many as 87% of women aged 25–69 years having had at least one Pap test within or outside the organised programme during the last 5 years. Outside the organised programme, the 5-year coverage was highest (75%) among women aged 25–29 years. Most of these Pap tests were taken in public primary health care. Furthermore, 44% of Pap tests taken in primary health care carried out for women aged 30 years or younger. When the organised programme starts at age 30, most of the women had already had a Pap test taken outside the organised programme.

Considering all Pap tests taken within and outside the organised screening, 44% of women aged 25–69 years had exactly one Pap test carried out during the last 5 years. Almost 50% of women aged 25–54 and one-third of women aged 55–69 had two or more Pap tests taken during the last 5 years. The proportion of women aged 25–69 years that had two or more Pap tests taken during the last 5 years decreased with age from 49% to 29%.

6 Discussion

6.1 Main results

This study shows the materials, methods, and results of economic evaluations of PCV7 (PCV7-I published in article I and PCV7-II previously unpublished) and influenza (II) vaccination programmes and the HPV-associated cost of illness study (III, IV), all of which were used in the vaccine adoption decision-making process in Finland in the period 2001–2011. The estimates produced for the disease burden and costs of HPV-related genital disease in women and the overall coverage, frequency and costs of Pap testing (III, IV) were further used as data in the HPV transmission and progression model and in the economic evaluations of the HPV vaccination programme and the screening for cervical cancer (217-219).

The infant PCV7 vaccination programme (excluding indirect herd effects) was not deemed cost-effective by the decision-makers at the anticipated vaccine price (PCV7-I). In the economic re-evaluation (PCV7-II), the indirect herd effects of the vaccination programme were included in older age groups, in which case the decision-makers found the infant PCV7 vaccination programme likely to be cost-effective on the basis of an assumed threshold of EUR 25 000 per QALY. Furthermore, the change from the 4- to 3-dose programme lowered the anticipated vaccination costs and improved the cost-effectiveness in the re-evaluation.

The influenza vaccination programme for healthy children was found to be cost saving from the health care provider perspective even though the indirect herd effects and influenza-associated deaths were excluded. The vaccination programme was estimated to save annually EUR 7.6 per vaccinated child aged 0.5–4 years when the assumed vaccine efficacy was 60%.

In Finland, there is a considerable annual disease burden of HPV-related genital disease in the female population. Most of it is detected by means of the 446 000 annual screening tests, 55% of which are carried out as opportunistic tests. It is noteworthy that the opportunistic tests account for 71% of the total of EUR 22.4 million screening costs (IV). Considering all tests taken both within and outside the organised programme, the 5-year coverage of Pap testing in Finland was 87% among women aged 25–69 years. Further diagnostics, management, and treatment of HPV-related genital disease resulted in an additional cost of EUR 22.3 million, of which the costs of less severe HPV-related disease manifestations were EUR 15.5 million (III).

6.2 Strengths and limitations

The high quality data sources is an evident strength of these studies. The incidences of AOM were obtained from a well-documented vaccine efficacy trial covering more than 50% of the birth cohort in the study area (44) and data on the frequency of Pap tests from comprehensive regional primary health care. CAP cared for solely in primary health care was the only disease category, the burden of which was estimated using several data sources. Except for the aforementioned outcomes, all other incidences of pneumococcal- and HPV-related disease were estimated from individual-level nationwide population-based register data. In the HPV dataset, the data sources were individually linkable even between the registers. The incidences of influenza-related outcomes were obtained from an epidemiological cohort study of laboratory-confirmed respiratory infections in children (108).

The heath-care-resource use due to disease outcomes was, with one exception (AOM), estimated from individual-level register data in the economic re-evaluation of the PCV7 vaccination programme (PCV7-II) and in the cost-of-illness study of HPV-related genital disease in women (III, IV). In the first economic evaluation of the PCV7 programme (PCV7-I) and in the economic evaluation of the influenza vaccination programme (II), the health care resource use was estimated from epidemiological studies, the regional hospital register, and according to expert opinion.

The lower burden of pneumococcal-related disease among children aged 0 to 4 years in the economic re-evaluation of the PCV7 programme (PCV7-II) compared to the first study (PCV7-I) is explained by a lower pneumonia incidence (10.3 per 1000), which was only one third of the incidence used in the first study (28.5 per 1000). This was mainly due to the differences in case definitions of pneumonia between studies: all-cause pneumonia in the first study (PCV7-I) and potentially pneumococcal pneumonia in the re-evaluation (PCV7-II). In the first study (PCV7-I), the incidence of pneumonia was obtained from a prospective regional epidemiological study conducted in 1981–1982 (34, 191). In the re-evaluation, the incidence of inpatient and outpatient pneumonia in secondary health care was estimated from individual-level register data (Hospital Discharge Register, 2001–2006) in which the pneumonia cases were retrieved with ICD-10 codes for pneumococcal (J13) or unspecified (J15.9, J18.1, J18.8 and J18.9) pneumonia. The total incidence of outpatient pneumonia was derived from the inpatient pneumonia incidence by assuming the proportions of inpatient and outpatient cases to be the same as in the Jokinen study (191). In the re-evaluation, the incidence of potentially pneumococcal pneumonia may have been underestimated, since pneumonia, like many other childhood illnesses, was most likely treated more often in inpatient care in the 1980s than in the 2000s (220). Compared to the first study (PCV7-I), the lower incidence of pneumonia in addition to the exclusion of the adenotomies from the analysis in the PCV7 re-evaluation (PCV7-II) resulted in markedly lower estimated health care costs without vaccinations.

In the PCV7 re-evaluation, in addition to the underestimated pneumonia incidence, the impact of the vaccination programme on pneumonia is likely to have been underestimated, since a low vaccine efficacy estimate of 4.3% (55) for all-cause pneumonia was applied to a more specific outcome of potentially pneumococcal pneumonia. In fact, PCV10 later showed an effectiveness of 27% against any hospital-diagnosed pneumonia, having an incidence as high as 13.3 per 1 000 person-years in infants followed on average for up to 27 months of age (35). However, in the vaccinated effects scenario (PCV7-II), this has a minor impact on the results. Even if the same pneumonia incidence and estimate for vaccine efficacy as in the first study (PCV7-I) were used, the cost per QALY gained would only decrease from EUR 83 759 to EUR 78 071 in the re-evaluation. In addition, we underestimated the costs of neurologic sequelae after meningitis by including only the first-year costs in the analysis.

In both economic evaluations of the PCV7 programme the direct vaccine efficacy estimates against IPD were not adjusted with the serotypes circulating in Finland. We used directly the vaccine efficacy estimates from the Northern Californian vaccine efficacy study, where the PCV7 serotype coverage of IPD in the control group was 89% (54). At the time the analyses were conducted, the serotyping results were not linked with the National Infectious Disease Register notifications and the estimated serotype distribution in Finland was expected to be imprecise. In Finland the National Infectious Disease Register notifications and the serotyping results have been linkable using the unique personal identity code only since 2004. Furthermore, it could be seen that adjusting VE with the estimated imprecise IPD serotype distribution was not influential on the results. Retrospectively it is possible to compare the data available at the time the analyses were conducted and the pre-vaccination period data. In Finland (1995–2002) the estimated PCV7 serotype coverage of IPD was 57%, 76% and 71% in children aged <1, 1, and 2–4 years, respectively (193). In the pre-vaccination period (2006–2008) in Finland, the estimated PCV7 serotype coverage of IPD was 77% in children aged <2 and 83% in children aged 2–4 years (National Infectious Diseases Register). The data in 2006–2008 has been validated in the FinIP trial (56). Although the vaccine serotype coverage and thus the direct vaccine effectiveness against IPD are likely to be overestimates in both economic evaluations, the influence on the results was minor. In the re-evaluation (PCV7-II), the proportion of estimated treatment costs saved due to IPD in total health care costs was 3%, and the proportion of QALYs gained due to IPD in total QALYs gained was 31%. Adjusting the direct effect according to the pre-vaccination serotype distribution in Finland would increase the cost per QALY gained from EUR 83 759 to EUR 87 209, when only the direct effect of the programme was taken into account.

In the indirect effects scenarios (PCV7-II), in addition to the direct effect we assumed the PCV7 vaccination programme to reduce 20% of the IPD cases (scenario A) or 20% of the IPD and 4% of the pneumonia cases treated in secondary health care (scenario B) in the unvaccinated population aged ≥5 years. Retrospectively, the assumed indirect herd effect was an overestimate in both scenarios. The impact of the PCV10 vaccination programme that started in September 2010 in Finland was estimated by comparing the incidence of IPD cases in pre- (2006–2008) and post-vaccination (2012–2014) periods. The incidence of IPD cases decreased in the unvaccinated population aged 5–49, aged 50–64 and aged ≥65 years by 20%,

5.0% and 5.2%, respectively (221). In an observational study comparing hospitalisation rates for pneumonia in Finland before (2004–2010) and after (2011–2014) the PCV7 programme was introduced, the incidence rates of hospital-treated pneumonia declined in the population aged 18–49, aged 50–64 and aged ≥65 years by 11.4%, 20.9% and 7.29%, respectively (222). However, these results may also be affected by other factors, such as influenza vaccinations, potential variation of pneumonia hospitalizations due to other pathogens, or changing coding practices. In other European countries, there is also evidence of serotype replacement that is resulting in a lower level of indirect protection. Assuming the PCV7 vaccination programme reduces 20% of the IPD cases (scenario A), this reduces the cost per QALY gained from EUR 83 759 to EUR 20 558. The reduction is mainly due to the incidence and case fatality ratio of IPD, both of which increase with age. If the incidence of IPD cases decreased in the unvaccinated population by only 5%, the cost per QALY gained would be EUR 49 600 at the vaccine prices of that time. However, the PCV10 vaccine was purchased for the NVP with a lower price than foreseen in the economic evaluations of PCV7 (PCV7-I, PCV7-II). In addition, a PCV10 effectiveness study has shown that the vaccination programme also reduced the incidence of clinically suspected non-laboratory-confirmed IPD in the vaccinated (56). Therefore, the PCV10 vaccination programme is most probably cost-saving from the health care provider perspective even at the lower level of the indirect herd effect.

Given the seasonal variation in influenza prevalence and the match between the vaccine and circulating subtypes of the virus, the influenza vaccine effectiveness varies from one influenza season to another (118, 122). In the base-case of the economic evaluation of influenza vaccination programme in children, we assumed the effectiveness of TIV to be 80% (II), which may be an overestimate for some of the seasons (122). Furthermore, the vaccination programme was cost-saving from the health care provider perspective even with a 60% vaccine efficacy. However, in some seasons, an even lower vaccine efficacy with a poor vaccine match with circulating viruses is possible.

In the economic evaluation of the influenza vaccination programme, we unrealistically assumed 100% vaccination coverage. In reality the coverage of the influenza vaccination programme in children <3 years of age is considerably lower. In the 2015–2016 season it was 24%. Thus, the potential total savings from the vaccination programme when assuming 100% vaccine coverage do not represent realistic estimates of the impact of the programme on the disease burden and costs. However, the expected cost-savings per vaccinated child is valid information for decision-making. In the economic evaluation, we made assumptions that were unfavourable for the vaccination programme: excluding influenza-associated deaths from the analysis and ignoring the herd effect. However, the exclusions did not jeopardize the decision-making, since even with these unfavourable assumptions, the vaccination programme was found to be cost-saving. We found that the cost of the vaccine was highly influential on the results.

This is the first study to reveal that the low cervical cancer incidence in Finland is not only due to the performance of organised screening but also due to extensive and expensive Pap testing occurring outside the organised screening programme (III, IV). Moreover, for the first time we showed the incidence and costs of the less severe HPV-related disease manifestations detected in Finland.

The estimates on how the disease outcomes affect health-related quality of life were obtained from the literature. It is noteworthy that because the data were scarce, QALY weights associated with disease outcomes were not age-dependent. This is an inaccurate assumption since the health-related quality of life is known to be age-dependent (203). However, the impact on QALYs gained is negligible in the economic evaluations of vaccination programmes in children, where only direct protection for a limited time is assumed. This was the case in the first economic evaluation of PCV7 (PCV7-I), in the vaccinated effects scenario in the re-evaluation (PCV7-II), and in the economic evaluation of influenza programme in children (II). Yet in the re-evaluation of the PCV7 vaccination programme, the QALYs gained in the indirect effects scenarios may be overestimated. However, this had a minor impact on the results, since the QALYs gained consisted mostly of life-years gained, which can been seen in the cost per QALY gained (EUR 20 558) and in the life-years gained (EUR 25 839), which were close to each other. It is noteworthy, that although the average health-related quality of life estimate (unrelated to a specific disease) declines with increasing age, the life years gained was estimated assuming that all life-years would have been lived in perfect health.

Despite EQ-5D and 15D being known to lead to different estimates of QALYs gained (203), we used estimates of these different instruments in assessing the health-related quality of life of the diseases. The 15D estimates were used for hearing defect related to pneumococcal meningitis and HPV-related cervical abnormalities (e.g. CIN and minor cytological abnormalities). Since QALYs gained related to pneumococcal meningitis was less than 1% of the total QALYs gained, the impact of using different instruments on the cost-effectiveness of the PCV7 vaccination programme was negligible. The 15D estimates (205) for HPV-related cervical abnormalities were somewhat lower than, for example, the trade-off (223) or EuroQol (224) estimates used in other studies. Nevertheless, the HPV vaccination programme has been estimated to be cost-saving in Finland even with the lower 15D estimates (219).

In order to be able to compare the costs of different diseases, all costs are presented in euros at the 2010 price level. Thus, the costs in the economic evaluations of the PCV7 and influenza vaccination programmes were transformed from values given in the original publications (I, II) or study (PCV7-II) according to the appropriate price indices. During the period between the time the economic evaluations of PCV7 were conducted (PCV7-I, PCV7-II) and 2010, the cost of the vaccine and health care costs in general changed in opposite directions: the cost of the vaccine has fallen and health care costs have risen. Our intention in this study was to summarise the results used in the decision-making at the time the vaccines were considered for inclusion in the NVP. Therefore, the cost of PCV7 was transformed with

the same consumer price index as the rest of the health care costs. If we had used the real cost of the vaccine in 2010, we would have altered the results and conclusions of the economic evaluations, since the vaccine price was an influential variable when estimating the cost-effectiveness of the vaccination programmes.

Most of the unit cost estimates in secondary health care (inpatient hospitalisation, outpatient visit) were estimated separately for specific disease-related outcomes (e. g. pneumococcal meningitis or cervical cancer) from individual-level cost accounting data from the Hospital District of Helsinki and Uusimaa. The secondary health care data collected in the studies included the cost accounting data for this single hospital district. In the first economic evaluation of the PCV7 programme, the unit cost estimates in secondary health care were partly obtained from the widely used National pricelist for unit costs of health care in Finland (197-199). In this pricelist, the unit costs are estimated from individual-level cost accounting data from 20 Hospital Districts in Finland for broader outcomes such as outpatient visit by speciality or inpatient hospitalisation by Diagnostic Related Groups classification system. The national pricelist for unit costs of health care in Finland is published by THL and updated every few years. The difference in the unit cost estimates of secondary health care in economic evaluations of the PCV7 programme (PCV7-I, PCV7-II) was due to inflation and these different sources for the estimates.

6.3 Comparison with other studies

In Europe, PCV7 came to the market in 2001. In the first economic evaluations, the vaccination programme was not reported to be acceptably cost-effective from the health care provider perspective at the vaccine prices of that time without taking into account the potential herd effects (81, 94, 96, 100). This finding is in line with our results (PCV7-I, PCV7-II).

There are many studies in which trivalent inactivated influenza vaccinations were reported to be cost-saving from the societal perspective (137-140). In addition to this study, at least Esposito and colleagues (134) have reported the influenza vaccinations to be cost-saving also from the health care payer perspective. In our study the cost for vaccine per dose (wholesale price) was considerably lower compared to other studies. Importantly, vaccine price for influenza vaccines used in the national programme was the most accurate variable used in our analysis.

In Finland, children aged 0 to 4 years experienced 250 000 episodes annually of all-cause otitis media, of which almost 16 000 were influenza-related (I, II). Otitis media was a driving factor when estimating the cost-effectiveness of the PCV7 programme (direct effects scenario) and the influenza vaccination programme in children. In fact, we estimated that almost 10 000 episodes of otitis media could potentially be prevented with either vaccination programme.

Finland appears to have the highest reported 5-year coverage of Pap testing among women aged 25–64 years in Europe when taking into account all Pap-tests within or outside the organised programme (166). However, countries starting the screening programme at the age of 25 or earlier and having a 3-year interval, might end up having a fairly similar Pap testing frequency to Finland.

Although the overall cervical cancer incidence is very low in Finland, the incidence among women aged 20 to 39 years has increased during the last 15 years (167, 225). The new finding of this study was the high Pap testing coverage among young women. Furthermore, the extensive Pap testing easily leads to unnecessary treatments. Preventing cervical cancer among young women by means of screening is difficult, since the HPV infection and precancerous lesions, which are highly likely to regress spontaneously, are most prevalent in women in their 20s and 30s. Therefore, among young women, HPV vaccinations that have been shown to reduce a considerable part of the HPV burden (169, 226) are the primary intervention in preventing cervical cancer and precancer.

In Finland, the National Advisory Committee on Vaccinations (KRAR) makes national recommendations on immunization policy. In many countries, there is an equivalent independent expert group, often called the national immunisation technical advisory group (NITAG). No less than 26 European countries report having a NITAG (227). The Finnish KRAR was established in 2001. The UK was among the first countries that established a NITAG: The British Joint Committee on Vaccination and Immunisation was established in 1963 (228). Of the European countries, 20 report to carry out a systematic vaccination decision-making process in which multiple criteria are considered (227). Among other, these criteria include estimating the epidemiology of vaccine preventable disease, the efficacy and safety of the vaccine, the effectiveness and cost-effectiveness of the vaccination programme, and the programme implementation. These criteria include also the criteria given by KRAR, according to which new vaccines are evaluated in Finland.

6.4 Implications for policymaking

The burden of disease and health care costs to providers always reflect the national health care system at that time. This could be seen in the detected cases of cervical cancer or CIN, which depend mainly on current Pap testing practices. At present, 60% of Pap tests are carried out outside the organised programme, from which 89% of cervical cancer cases and 80% of CIN cases are detected in Finland (229). Thus, the successful reduction in cervical cancer incidence and mortality is due to tests taken both within and outside the organised screening. The opportunistic Pap testing both substitutes and overlaps with the tests taken in the organised programme. Overlapping tests stem from the lack of coordination between organised and opportunistic Pap testing and results in over-management of reversible lesions. In order to be able to coordinate organised and opportunistic Pap testing, it is essential to establish a nationwide Pap test register. Furthermore, such a register is necessary for effective and cost-effective secondary prevention of cervical cancer, which will be needed in both unvaccinated and vaccinated populations.

The high Pap testing coverage among young women is a result of their repeated contacts with several health care providers. In addition to organised screening, women aged <39 years are tested in public primary, student, and private health care. It is important not to lose the high coverage when trying to achieve reductions in overlapping Pap testing. This is one additional reason why it is essential to establish a nationwide Pap test register that is accessible to all health care providers.

In Finland, the economic evaluation of the vaccination programme has been part of the decision-making process since 2001. After 2003 there are five vaccinations that have been considered for the Finnish NVP and for which an economic evaluation has been conducted. Vaccinations of all children aged 6–36 months with influenza vaccine were estimated to be cost-saving (II) and the vaccine was accepted into the NVP in 2007. Infant's rotavirus and pneumococcal vaccinations were accepted into the NVP in 2008 and 2010 with a cost per QALY gained of EUR 25 000 (230, 231) and EUR 20 490 (232), respectively. Vaccinations of all girls aged 11–13 years with HPV vaccine was estimated to be cost-saving (219) and was accepted into the NVP in 2013. Varicella vaccinations were concluded to be acceptably cost-effective with a cost per QALY gained of EUR 15 000 (233). Vaccinations were included in the Government's budget proposal in August 2016 and they will start in 2017. All these results of economic evaluations are from the health care provider perspective.

In Finland, the prices at which vaccines are finally purchased for the NVP are not known in advance. However, the prices are as a rule below the pharmacy price due to the centralised purchasing system and a competitive tendering process. The prices at which vaccines against rotavirus, pneumococcus and HPV were eventually purchased for the NVP were lower than the anticipated price that was used in the economic evaluations. Actually, both rotavirus and pneumococcal vaccinations are expected to be cost-saving from the health care provider perspective with the post-vaccination effectiveness (72, 234) and actualised vaccine prices.

6.5 Unanswered questions and directions for the future

The studies presented were all conducted for the decision-making process for adopting potential new vaccines in the NVP. However, an assessment only prior to vaccine introduction is not sufficient. Continuous assessment of both post-implementation effectiveness and cost-effectiveness of the publicly funded vaccination programmes is equally important (235). In retrospective economic evaluations, the sources of uncertainty can be reduced and therefore the estimates for cost-effectiveness might be more reliable. The impact of the vaccination programme can be confirmed or challenged by the post-implementation surveillance of the direct and indirect herd effects of the programme and vaccination coverage. In addition, the price at which the vaccine was actually purchased for the NVP is known. For example, the current price for PCV10 is considerably lower than the assumed price of the PCV7 in the pre-implementation economic evaluations. When new vaccine products arrive in the market the up-to-date detailed data on the burden of disease are important in comparing the products. It is also possible that there is a need to reassess the target groups of the vaccinations. An invitation to tender is put out every 2–3 years for each vaccine. Economic evaluations need to be updated also for these competitive tendering processes, where the economic evaluation is used in setting evaluation criteria for tender specification for the vaccine.

In Finland, decision-makers have not specified an explicit threshold for cost-effectiveness, below which an intervention or programme would automatically be accepted and lead to funding. However, an explicit range of cost-effectiveness threshold values would improve the transparency in decision-making and would therefore be highly advisable. The process of adopting a new vaccine into the national vaccination programme provides an established roadmap for decision-making in health care. In this process, an economic evaluation serves as an indispensable node.

7 Conclusions

1. Since resources are scarce, new health care interventions need to be carefully considered. In Finland, the development of the national vaccination programme (NVP) is based on four criteria: expected public health benefit, safety of a vaccine for an individual, safety of the programme at the population level, and its cost-effectiveness. It is not self-evident that introducing a new vaccine into the NVP is making the most of our common resources.

2. Economic evaluations are needed to support the decision-making process so that decision-makers are informed and able to choose from among potential alternatives. Likewise, economic evaluations are needed for a competitive tendering process when purchasing vaccines for the NVP. In Finland, economic evaluations of vaccination programmes have been part of the decision-making process since 2001. Assessing an explicit threshold range for cost-effectiveness, below which an intervention would be accepted and lead to funding would improve the transparency in decision-making and therefore would be highly advisable.

3. The PCV7 vaccination programme was found to be cost-effective when taking into account the direct and indirect herd effects of the vaccination programme. However, more recent data on observed indirect effect suggests that expected herd effects have not been observed, unlike the direct effects, which appear better than expected.

4. The influenza vaccination programme of children aged 6 months to 13 years was estimated to be cost-saving from the health care provider perspective with the 60% vaccine efficacy. The price of vaccine, the influenza incidence and the vaccine efficacy were highly influential on the results of the cost-effectiveness analysis. However, there is considerable seasonal variability in influenza epidemics and in the match between the vaccine and circulating subtypes of the virus.

5. There is a considerable disease burden of HPV-related genital disease in the female population in Finland. The detection of cervical cancer or CIN is highly dependent on the current Pap testing practices. At present, 60% of Pap tests are carried out outside the organised programme, from which 89% of cervical cancer cases and 80% of CIN cases are detected.

6. The 5-year coverage of Pap testing in Finland is very high (87%) when tests taken both within and outside the organised programme are taken into account. Opportunistic Pap testing both substitutes and overlaps with tests carried out in the organised programme. Overlapping tests stem from a lack of coordination between organised and opportunistic Pap testing and result in over-management of reversible lesions. It is critical not to lose the high coverage when trying to achieve reductions in overlapping Pap testing. In order to be able to coordinate the organised and opportunistic Pap testing and develop a cost-effective strategy for the secondary prevention of cervical cancer, it is essential to establish a nationwide Pap test register.

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